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Anesthesia and Analgesia

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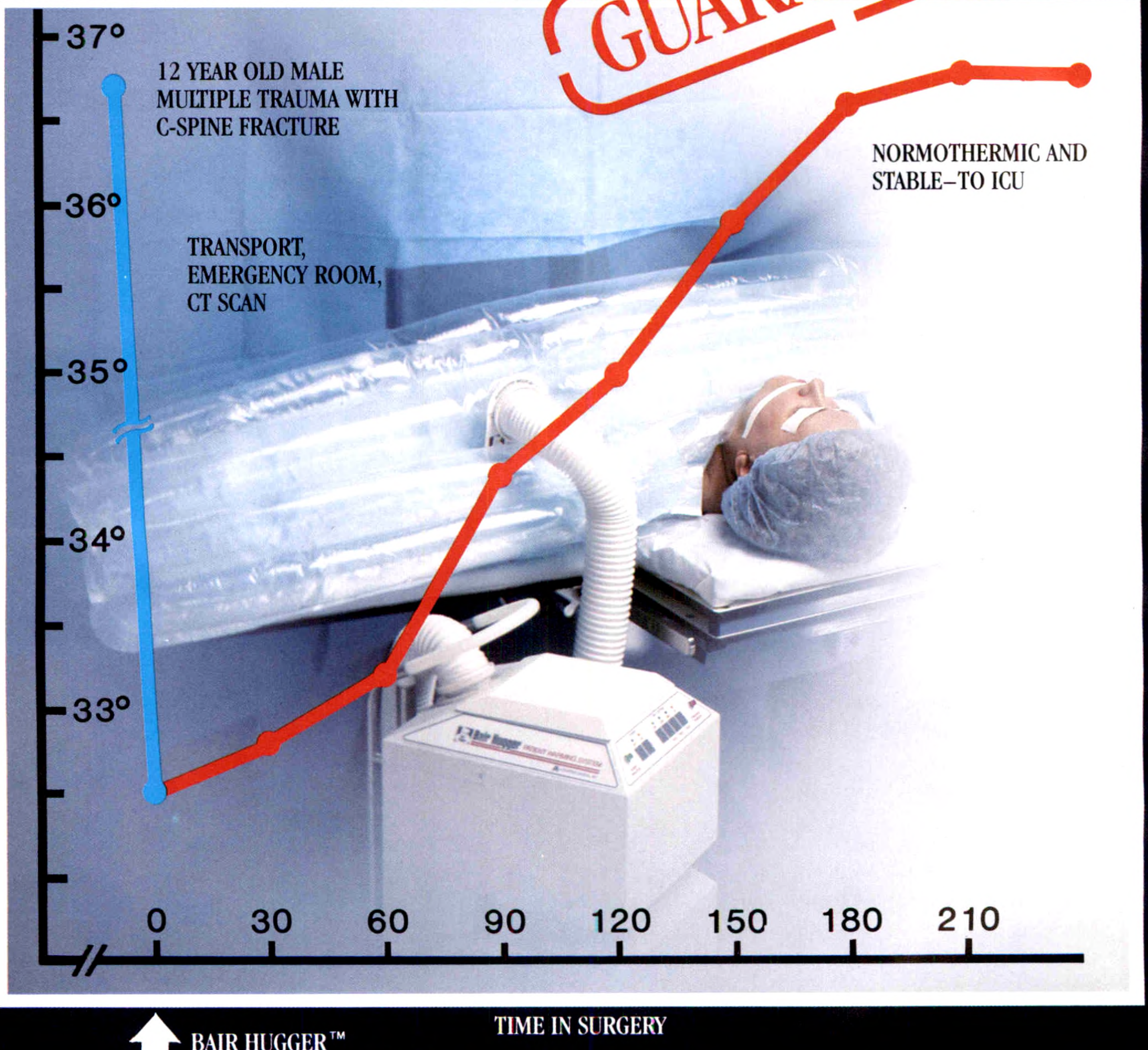

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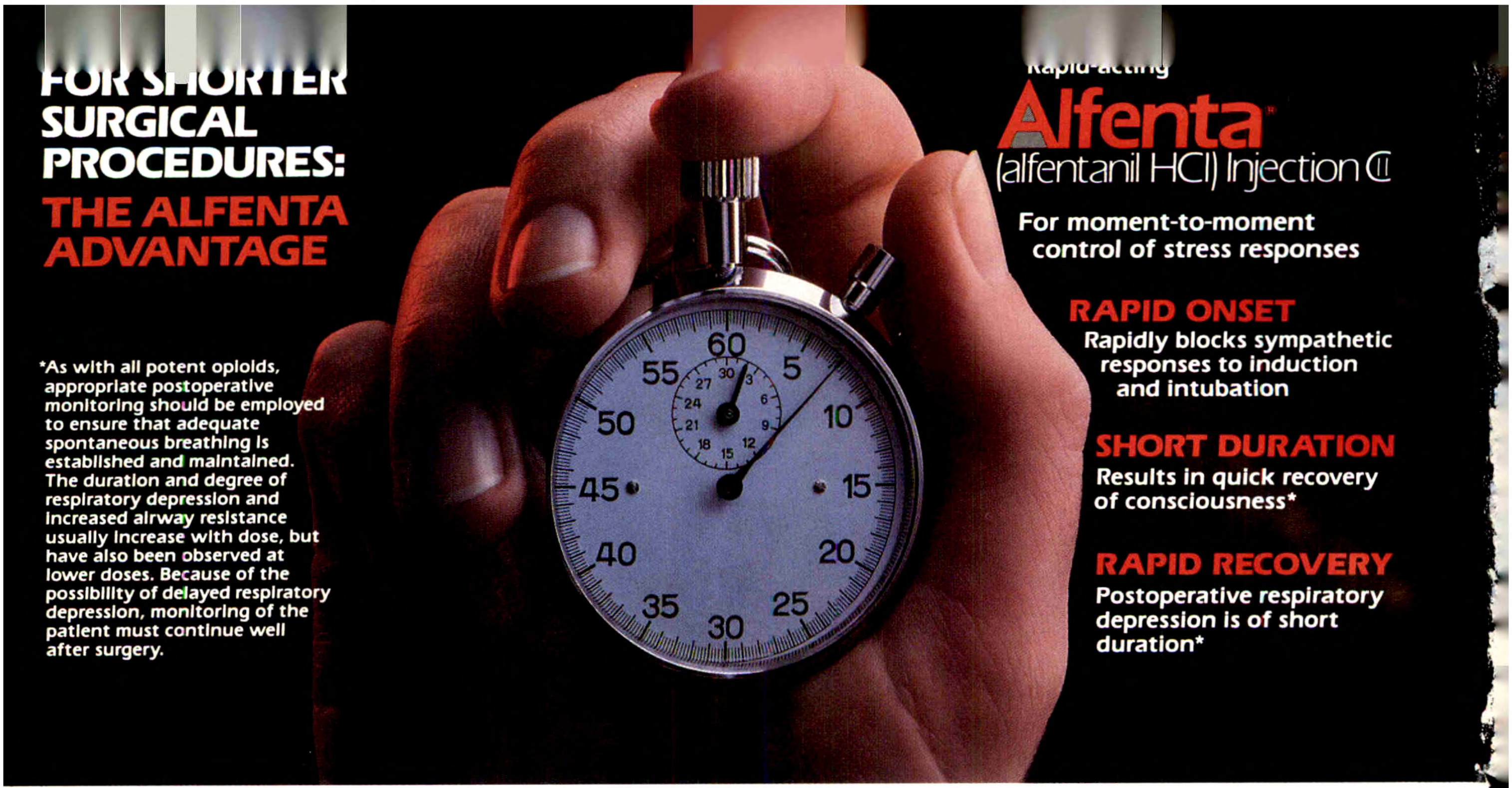

FOR SHORTER SURGICAL PROCEDURES: THE ALFENTA ADVANTAGE

*As with all potent opioids, appropriate postoperative monitoring should be employed to ensure that adequate spontaneous breathing is established and maintained. The duration and degree of respiratory depression and increased airway resistance usually increase with dose, but have also been observed at lower doses. Because of the possibility of delayed respiratory depression, monitoring of the patient must continue well after surgery.

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CAUTION: Federal Law Prohibits Dispensing Without Prescription
DESCRIPTION: ALFENTA is a sterile, non-pyrogenic, preservative free aqueous solution containing alfentanil hydrochloride equivalent to 500 µg per ml of alfentanil base for intravenous injection. The solution, which contains sodium chloride for isotonicity, has a pH range of 4.0-6.0.
CONTRAINDICATIONS: ALFENTA (alfentanil hydrochloride) is contraindicated in patients with known hypersensitivity to the drug.
WARNINGS: ALFENTA SHOULD BE ADMINISTERED ONLY BY PERSONS SPECIFICALLY TRAINED IN THE USE OF INTRAVENOUS AND GENERAL ANESTHETIC AGENTS AND IN THE MANAGEMENT OF RESPIRATORY EFFECTS OF POTENT OPIOIDS. AN OPIOID ANTAGONIST, RESUSCITATIVE AND INTUBATION EQUIPMENT AND OXYGEN SHOULD BE READILY AVAILABLE. BECAUSE OF THE POSSIBILITY OF DELAYED RESPIRATORY DEPRESSION, MONITORING OF THE PATIENT MUST CONTINUE WELL AFTER SURGERY. ALFENTA (alfentanil hydrochloride) administered in initial dosages up to 20 µg/kg may cause skeletal muscle rigidity, particularly of the truncal muscles. The incidence and severity of muscle rigidity is usually dose-related. Administration of ALFENTA at anesthetic induction dosages (above 130 µg/kg) will consistently produce muscular rigidity with an immediate onset. The onset of muscular rigidity occurs earlier than with other opioids. ALFENTA may produce muscular rigidity that involves all skeletal muscles, including those of the neck and extremities. The incidence may be reduced by: 1) routine methods of administration of neuromuscular blocking agents for balanced opioid anesthesia; 2) administration of up to ¼ of the full paralyzing dose of a neuromuscular blocking agent just prior to administration of ALFENTA at dosages up to 130 µg/kg; following loss of consciousness, a full paralyzing dose of a neuromuscular blocking agent should be administered; or 3) simultaneous administration of ALFENTA and a full paralyzing dose of a neuromuscular blocking agent when ALFENTA is used in rapidly administered anesthetic dosages (above 130 µg/kg). The neuromuscular blocking agent used should be appropriate for the patient's cardiovascular status. Adequate facilities should be available for postoperative monitoring and ventilation of patients administered ALFENTA. It is essential that these facilities be fully equipped to handle all degrees of respiratory depression.
PRECAUTIONS: DELAYED RESPIRATORY DEPRESSION, RESPIRATORY ARREST, BRADYCARDIA, ASYSTOLE, ARRHYTHMIAS AND HYPOTENSION HAVE ALSO BEEN REPORTED. THEREFORE, VITAL SIGNS MUST BE MONITORED CONTINUOUSLY.
General: The initial dose of ALFENTA (alfentanil hydrochloride) should be appropriately reduced in elderly and debilitated patients. The effect of the initial dose should be considered in determining supplemental doses. In obese patients (more than 20% above ideal total body weight), the dosage of ALFENTA should be determined on the basis of lean body weight. In one clinical trial, the dose of ALFENTA required to produce anesthesia, as determined by appearance of delta waves in EEG, was 40% lower in geriatric patients than that needed in healthy young patients. In patients with compromised liver function and in geriatric patients, the plasma clearance of ALFENTA may be reduced and postoperative recovery may be prolonged. Induction doses of ALFENTA should be administered slowly (over three minutes). Administration may produce loss of vascular tone and hypotension. Consideration should be given to fluid replacement prior to induction. Diazepam administered immediately prior to or in conjunction with high doses of ALFENTA may produce vasodilation, hypotension and result in delayed recovery. Bradycardia produced by ALFENTA may be treated with atropine. Severe bradycardia and asystole have been successfully treated with atropine and conventional resuscitative methods. The hemodynamic effects of a particular muscle relaxant and the degree of skeletal muscle relaxation required should be considered in the selection of a neuromuscular blocking agent. Following an anesthetic induction dose of ALFENTA, requirements for volatile inhalation anesthetics or ALFENTA infusion are reduced by 30 to 50% for the first hour of maintenance. Administration of ALFENTA infusion should be discontinued at leas 10-15 minutes prior to the end of surgery. Respiratory depression caused by opioid analgesics can be reversed by opioid antagonists such as naloxone. Because the duration of respiratory depression produced by ALFENTA may last longer than the duration of the opioid antagonist action, appropriate surveillance should be maintained. As with all potent opioids, profound analgesia is accompanied by respiratory depression and diminished sensitivity to CO_2 stimulation which may persist into or recur in the postoperative period. Intraoperative hyperventilation may further alter postoperative response to CO_2. Appropriate postoperative monitoring should be employed, particularly after infusions and large doses of ALFENTA, to ensure that adequate spontaneous breathing is established and maintained in the absence of stimulation prior to discharging the patient from the recovery area.
Head Injuries: ALFENTA may obscure the clinical course of patients with head injuries.
Impaired Respiration: ALFENTA should be used with caution in patients with pulmonary disease, decreased respiratory reserve or potentially compromised respiration. In such patients, opioids may additionally decrease respiratory drive and increase airway resistance. During anesthesia, this can be managed by assisted or controlled respiration.
Impaired Hepatic or Renal Function: In patients with liver or kidney dysfunction, ALFENTA should be administered with caution due to the importance of these organs in the metabolism and excretion of ALFENTA.
Drug Interactions: Both the magnitude and duration of central nervous system and cardiovascular effects may be enhanced when ALFENTA is administered in combination with other CNS depressants such as barbiturates, tranquilizers, opioids, or inhalation general anesthetics. Postoperative respiratory depression may be enhanced or prolonged by these agents. In such cases of combined treatment, the dose of one or both agents should be reduced. Limited clinical experience indicates that requirements for volatile inhalation anesthetics are reduced by 30 to 50% for the first sixty (60) minutes following ALFENTA induction. The concomitant use of erythromycin with ALFENTA can significantly inhibit ALFENTA clearance and may increase the risk of prolonged or delayed respiratory depression. Perioperative administration of drugs affecting hepatic blood flow or enzyme function may reduce plasma clearance and prolong recovery.
Carcinogenesis, Mutagenesis and Impairment of Fertility: No long-term animal studies of ALFENTA have been performed to evaluate carcinogenic potential. The micronucleus test in female rats and the dominant lethal test in female and male mice revealed that single intravenous doses of ALFENTA as high as 20 mg/kg (approximately 40 times the upper human dose) produced no structural chromosome mutations or induction of dominant lethal mutations. The Ames *Salmonella typhimurium* metabolic activating test also revealed no mutagenic activity.
Pregnancy Category C: ALFENTA has been shown to have an embryocidal effect in rats and rabbits when given in doses 2.5 times the upper human dose for a period of 10 days to over 30 days. These effects could have been due to maternal toxicity (decreased food consumption with increased mortality) following prolonged administration of the drug. No evidence of teratogenic effects has been observed after administration of ALFENTA in rats or rabbits. There are no adequate and well-controlled studies in pregnant women. ALFENTA should be used during pregnancy only if the potential benefit justifies the potential risk to the fetus.
Labor and Delivery: There are insufficient data to support the use of ALFENTA in labor and delivery. Placental transfer of the drug has been reported; therefore, use in labor and delivery is not recommended.
Nursing Mothers: In one study of nine women undergoing post-partum tubal ligation, significant levels of ALFENTA were detected in colostrum four hours after administration of 60 µg/kg of ALFENTA, with no detectable levels present after 28 hours. Caution should be exercised when ALFENTA is administered to a nursing woman.
Pediatric Use: Adequate data to support the use of ALFENTA in children under 12 years of age are not presently available.
ADVERSE REACTIONS: The most common adverse reactions, respiratory depression and skeletal muscle rigidity, are extensions of known pharmacological effects of opioids. See CLINICAL PHARMACOLOGY, WARNINGS and PRECAUTIONS on the management of respiratory depression and skeletal muscle rigidity. Delayed respiratory depression, respiratory arrest, bradycardia, asystole, arrhythmias and hypotension have also been reported. The reported incidences of adverse reactions listed in the following table are derived from controlled and open clinical trials involving 1183 patients, of whom 785 received ALFENTA. The controlled trials involved treatment comparisons with fentanyl, thiopental sodium, enflurane, saline placebo and halothane. Incidences are based on disturbing and nondisturbing adverse reactions reported. The comparative incidence of certain side effects is influenced by the type of use, e.g., chest wall rigidity has a higher reported incidence in clinical trials of alfentanil induction, and by the type of surgery, e.g., nausea and vomiting have a higher incidence in patients undergoing gynecologic surgery.

Percent	ALFENTA (N=785)	Fentanyl (N=243)	Thiopental Sodium (N=66)	Enflurane (N=55)	Halothane (N=18)	Saline Placebo* (N=18)
Gastrointestinal						
Nausea	28	44	14	5	0	22
Vomiting	18	31	11	9	13	17
Cardiovascular						
Bradycardia	14	7	8	0	0	0
Tachycardia	12	12	39	36	31	11
Hypotension	10	8	7	7	0	0
Hypertension	18	13	30	20	6	0
Arrhythmia	2	2	5	4	6	0
Musculoskeletal						
Chest Wall Rigidity	17	12	0	0	0	0
Skeletal Muscle Movements	6	2	6	2	0	0
Respiratory						
Apnea	7	0	0	0	0	0
Postoperative Respiratory Depression	2	2	0	0	0	0
CNS						
Dizziness	3	5	0	0	0	0
Sleepiness/Postoperative Sedation	2	8	2	0	0	6
Blurred Vision	2	2	0	0	0	0

*From two clinical trials, one involving supplemented balanced barbiturate / nitrous oxide anesthesia and one in healthy volunteers who did not undergo surgery.

In addition, other adverse reactions less frequently reported (1% or less) were: Laryngospasm, bronchospasm, postoperative confusion, headache, shivering, postoperative euphoria, hypercarbia, pain on injection, urticaria, and itching. Some degree of skeletal muscle rigidity should be expected with induction doses of ALFENTA.
DRUG ABUSE AND DEPENDENCE: ALFENTA (alfentanil hydrochloride) is a Schedule II controlled drug substance that can produce drug dependence of the morphine type and therefore has the potential for being abused.
OVERDOSAGE: Overdosage would be manifested by extension of the pharmacological actions of ALFENTA (alfentanil hydrochloride) (see CLINICAL PHARMACOLOGY) as with other potent opioid analgesics. No experience of overdosage with ALFENTA was reported during clinical trials. The intravenous LD_{50} of ALFENTA is 43.0-50.9 mg/kg in rats, 72.2-73.6 mg/kg in mice, 71.8-81.9 mg/kg in guinea pigs and 59.5-87.5 mg/kg in dogs. Intravenous administration of an opioid antagonist such as naloxone should be employed as a specific antidote to manage respiratory depression. The duration of respiratory depression following overdosage with ALFENTA may be longer than the duration of action of the opioid antagonist. Administration of an opioid antagonist should not preclude immediate establishment of a patent airway, administration of oxygen, and assisted or controlled ventilation as indicated for hypoventilation or apnea. If respiratory depression is associated with muscular rigidity, a neuromuscular blocking agent may be required to facilitate assisted or controlled ventilation. Intravenous fluids and vasoactive agents may be required to manage hemodynamic instability.
DOSAGE AND ADMINISTRATION: The dosage of ALFENTA (alfentanil hydrochloride) should be individualized in each patient according to body weight, physical status, underlying pathological condition, use of other drugs, and type and duration of surgical procedure and anesthesia. In obese patients (more than 20% above ideal total body weight), the dosage of ALFENTA should be determined on the basis of lean body weight. The dose of ALFENTA should be reduced in elderly or debilitated patients (see PRECAUTIONS). Vital signs should be monitored routinely. Protect from light. Store at room temperature 15°-30° C (59°-86° F).

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March 1987, April 1988
U.S. Patent No. 4,167,574
49-7619902-M

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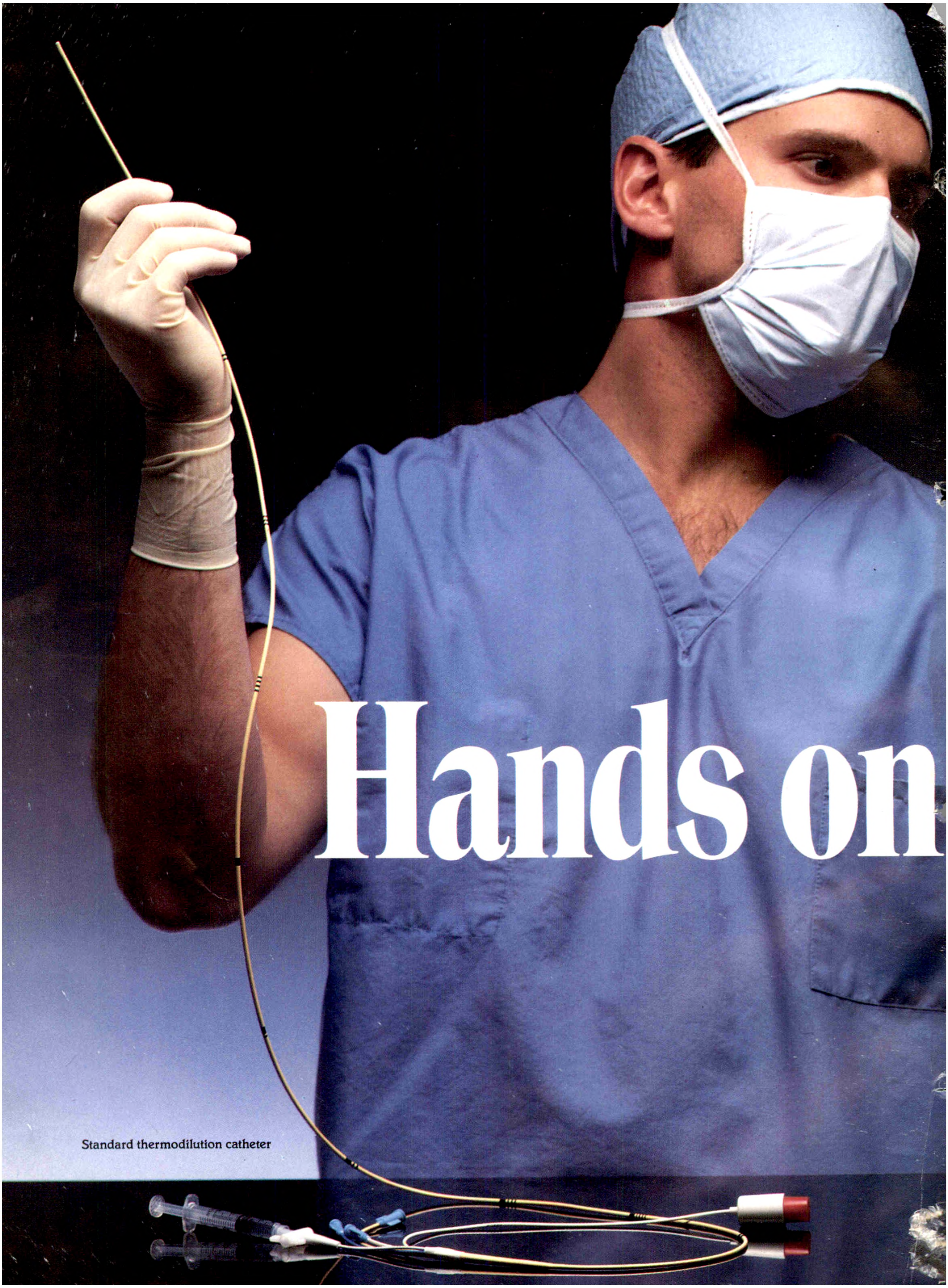
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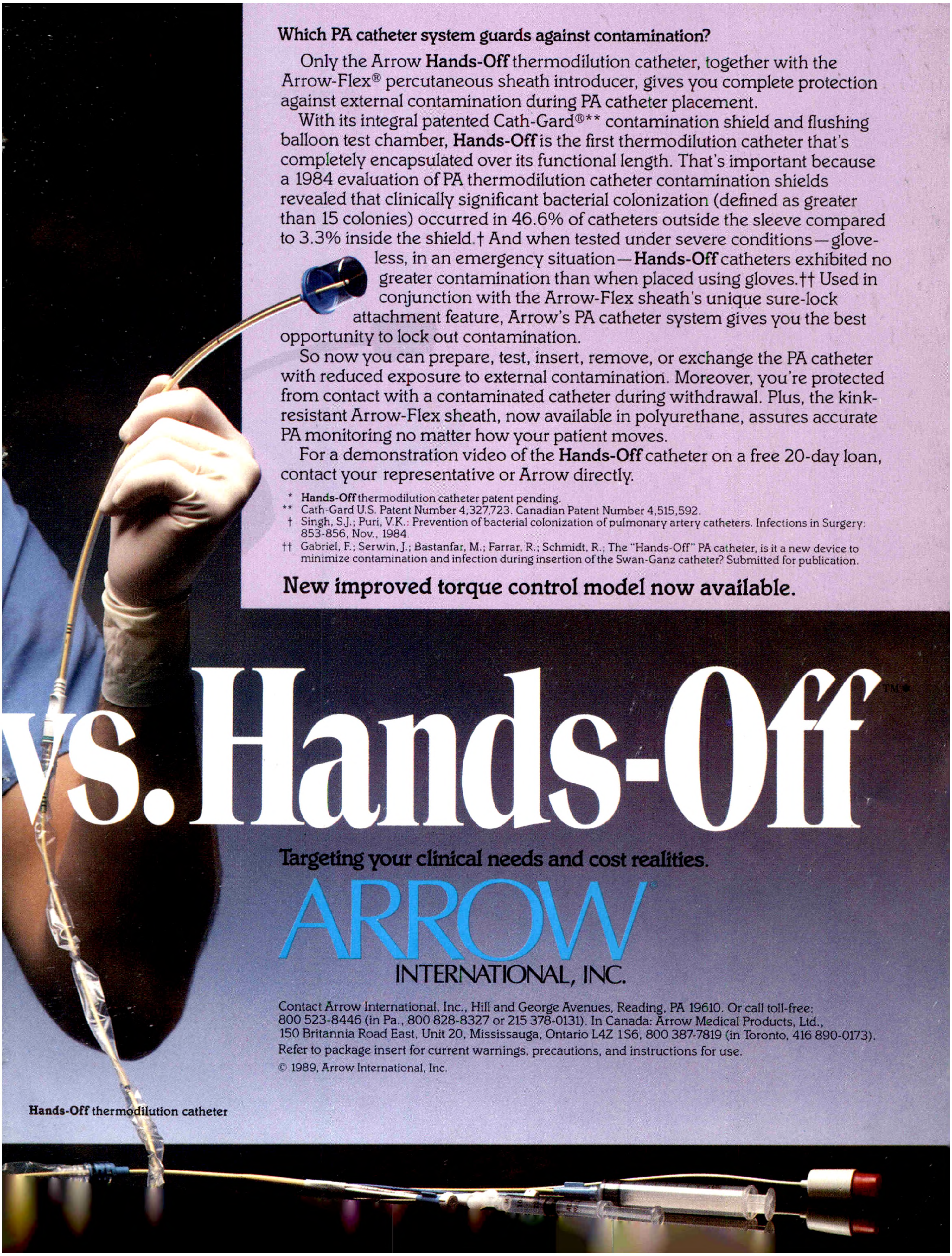

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* **Hands-Off** thermodilution catheter patent pending.

** Cath-Gard U.S. Patent Number 4,327,723. Canadian Patent Number 4,515,592.

† Singh, S.J.; Puri, V.K.: Prevention of bacterial colonization of pulmonary artery catheters. Infections in Surgery: 853-856, Nov., 1984.

†† Gabriel, F.; Serwin, J.; Bastanfar, M.; Farrar, R.; Schmidt, R.; The "Hands-Off" PA catheter, is it a new device to minimize contamination and infection during insertion of the Swan-Ganz catheter? Submitted for publication.

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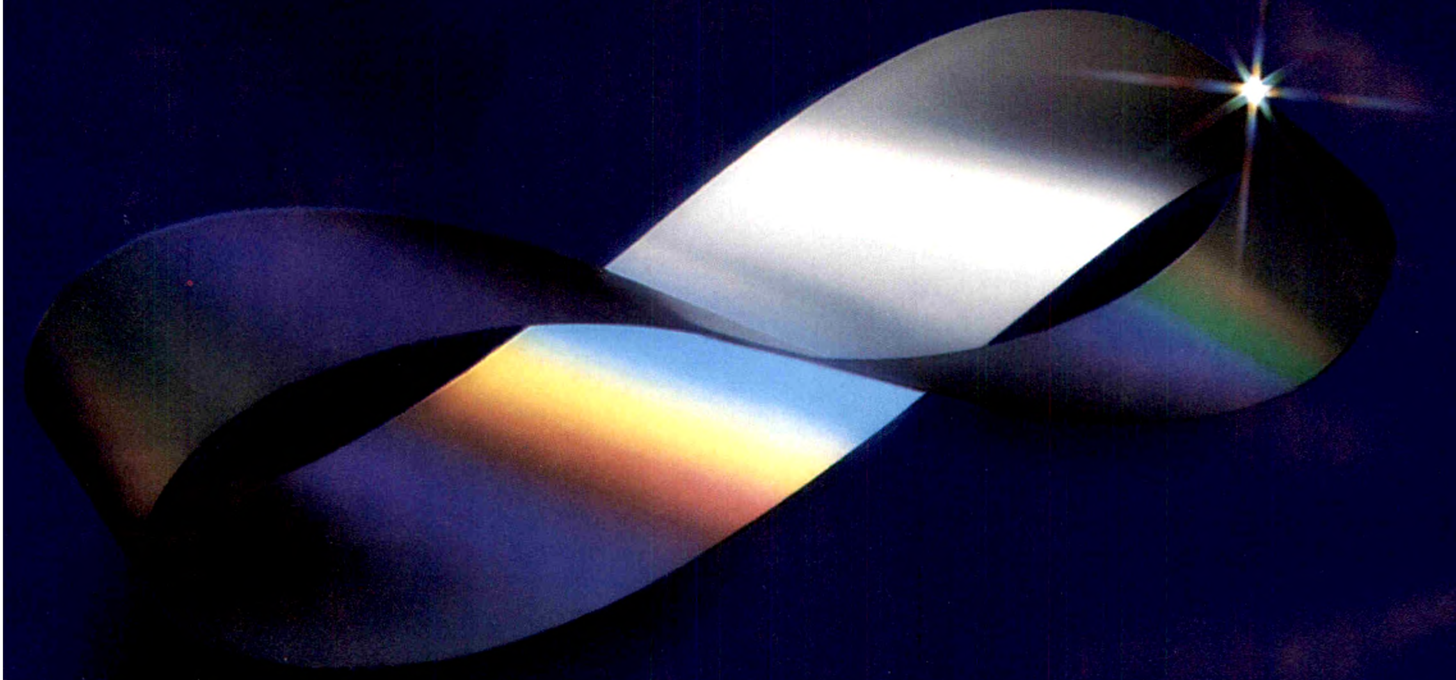

Anesthesia and Analgesia

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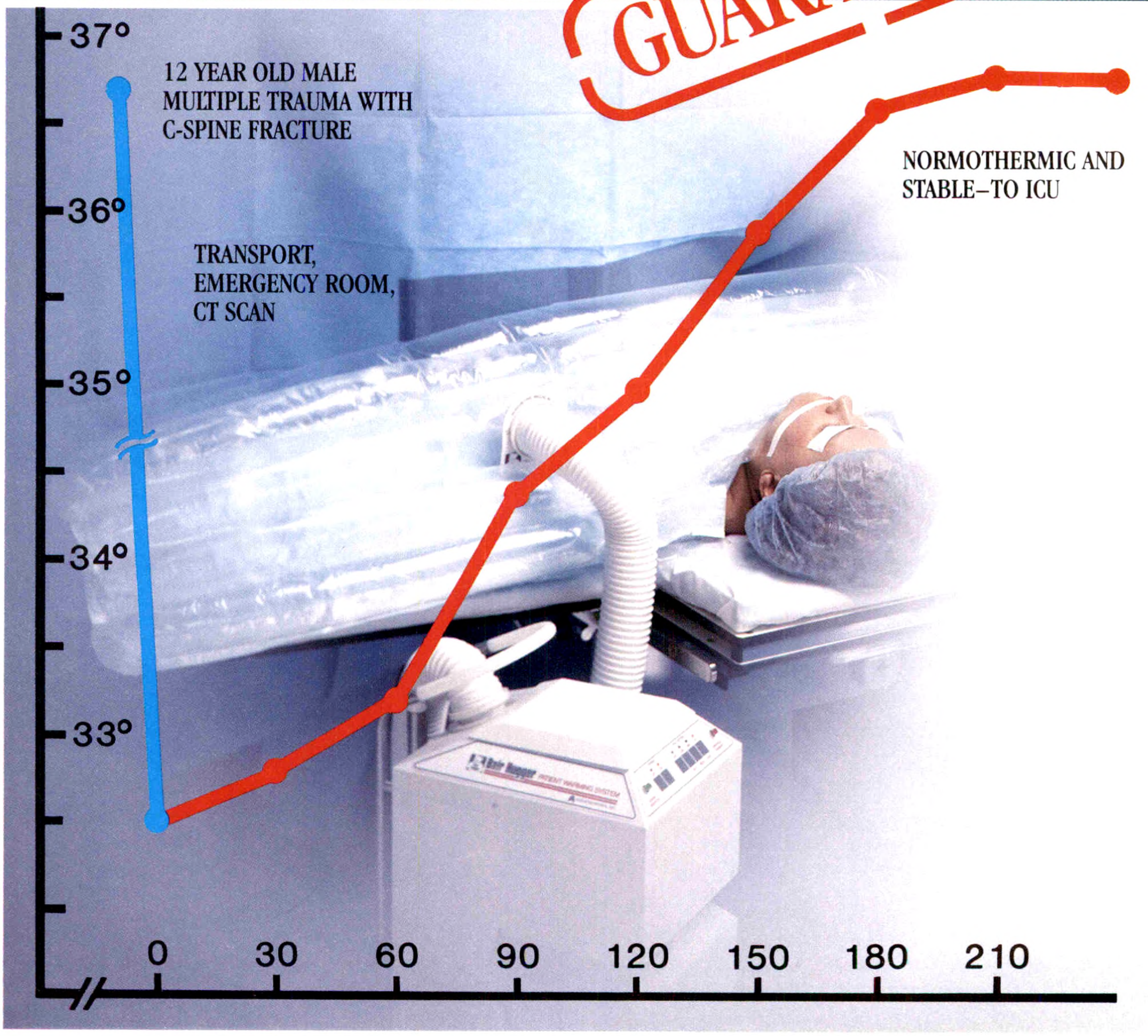

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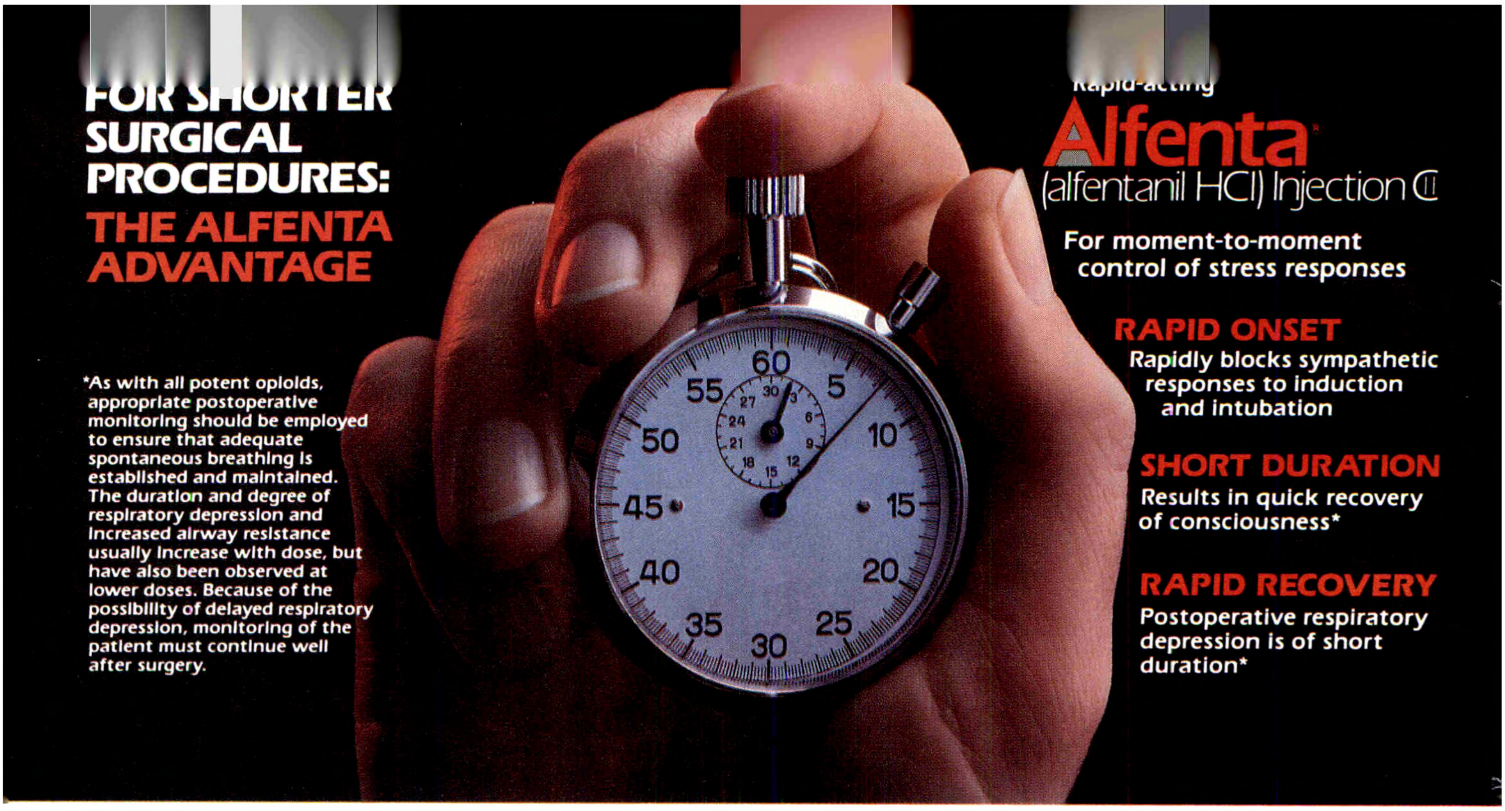
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CONTRAINDICATIONS: ALFENTA (alfentanil hydrochloride) is contraindicated in patients with known hypersensitivity to the drug.
WARNINGS: ALFENTA SHOULD BE ADMINISTERED ONLY BY PERSONS SPECIFICALLY TRAINED IN THE USE OF INTRAVENOUS AND GENERAL ANESTHETIC AGENTS AND IN THE MANAGEMENT OF RESPIRATORY EFFECTS OF POTENT OPIOIDS. AN OPIOID ANTAGONIST, RESUSCITATIVE AND INTUBATION EQUIPMENT AND OXYGEN SHOULD BE READILY AVAILABLE. BECAUSE OF THE POSSIBILITY OF DELAYED RESPIRATORY DEPRESSION, MONITORING OF THE PATIENT MUST CONTINUE WELL AFTER SURGERY. ALFENTA (alfentanil hydrochloride) administered in initial dosages up to 20 μg/kg may cause skeletal muscle rigidity, particularly of the truncal muscles. The incidence and severity of muscle rigidity is usually dose-related. Administration of ALFENTA at anesthetic induction dosages (above 130 μg/kg) will consistently produce muscular rigidity with an immediate onset. The onset of muscular rigidity occurs earlier than with other opioids. ALFENTA may produce muscular rigidity that involves all skeletal muscles, including those of the neck and extremities. The incidence may be reduced by: 1) routine methods of administration of neuromuscular blocking agents for balanced opioid anesthesia; 2) administration of up to ¼ of the full paralyzing dose of a neuromuscular blocking agent just prior to administration of ALFENTA at dosages up to 130 μg/kg; following loss of consciousness, a full paralyzing dose of a neuromuscular blocking agent should be administered; or 3) simultaneous administration of ALFENTA and a full paralyzing dose of a neuromuscular blocking agent when ALFENTA is used in rapidly administered anesthetic dosages (above 130 μg/kg). The neuromuscular blocking agent used should be appropriate for the patient's cardiovascular status. Adequate facilities should be available for postoperative monitoring and ventilation of patients administered ALFENTA. It is essential that these facilities be fully equipped to handle all degrees of respiratory depression.
PRECAUTIONS: DELAYED RESPIRATORY DEPRESSION, RESPIRATORY ARREST, BRADYCARDIA, ASYSTOLE, ARRHYTHMIAS AND HYPOTENSION HAVE ALSO BEEN REPORTED. THEREFORE, VITAL SIGNS MUST BE MONITORED CONTINUOUSLY.
General: The initial dose of ALFENTA (alfentanil hydrochloride) should be appropriately reduced in elderly and debilitated patients. The effect of the initial dose should be considered in determining supplemental doses. In obese patients (more than 20% above ideal total body weight), the dosage of ALFENTA should be determined on the basis of lean body weight. In one clinical trial, the dose of ALFENTA required to produce anesthesia, as determined by appearance of delta waves in EEG, was 40% lower in geriatric patients than that needed in healthy young patients. In patients with compromised liver function and in geriatric patients, the plasma clearance of ALFENTA may be reduced and postoperative recovery may be prolonged. Induction doses of ALFENTA should be administered slowly (over three minutes). Administration may produce loss of vascular tone and hypotension. Consideration should be given to fluid replacement prior to induction. Diazepam administered immediately prior to or in conjunction with high doses of ALFENTA may produce vasodilation, hypotension and result in delayed recovery. Bradycardia produced by ALFENTA may be treated with atropine. Severe bradycardia and asystole have been successfully treated with atropine and conventional resuscitative methods. The hemodynamic effects of a particular muscle relaxant and the degree of skeletal muscle relaxation required should be considered in the selection of a neuromuscular blocking agent. Following an anesthetic induction dose of ALFENTA, requirements for volatile inhalation anesthetics or ALFENTA infusion are reduced by 30 to 50% for the first hour of maintenance. Administration of ALFENTA infusion should be discontinued at leas 10-15 minutes prior to the end of surgery. Respiratory depression caused by opioid analgesics can be reversed by opioid antagonists such as naloxone. Because the duration of respiratory depression produced by ALFENTA may last longer than the duration of the opioid antagonist action, appropriate surveillance should be maintained. As with all potent opioids, profound analgesia is accompanied by respiratory depression and diminished sensitivity to CO_2 stimulation which may persist into or recur in the postoperative period. Intraoperative hyperventilation may further alter postoperative response to CO_2. Appropriate postoperative monitoring should be employed, particularly after infusions and large doses of ALFENTA, to ensure that adequate spontaneous breathing is established and maintained in the absence of stimulation prior to discharging the patient from the recovery area.
Head Injuries: ALFENTA may obscure the clinical course of patients with head injuries.
Impaired Respiration: ALFENTA should be used with caution in patients with pulmonary disease, decreased respiratory reserve or potentially compromised respiration. In such patients, opioids may additionally decrease respiratory drive and increase airway resistance. During anesthesia, this can be managed by assisted or controlled respiration.
Impaired Hepatic or Renal Function: In patients with liver or kidney dysfunction, ALFENTA should be administered with caution due to the importance of these organs in the metabolism and excretion of ALFENTA.
Drug Interactions: Both the magnitude and duration of central nervous system and cardiovascular effects may be enhanced when ALFENTA is administered in combination with other CNS depressants such as barbiturates, tranquilizers, opioids, or inhalation general anesthetics. Postoperative respiratory depression may be enhanced or prolonged by these agents. In such cases of combined treatment, the dose of one or both agents should be reduced. Limited clinical experience indicates that requirements for volatile inhalation anesthetics are reduced by 30 to 50% for the first sixty (60) minutes following ALFENTA induction. The concomitant use of erythromycin with ALFENTA can significantly inhibit ALFENTA clearance and may increase the risk of prolonged or delayed respiratory depression. Perioperative administration of drugs affecting hepatic blood flow or enzyme function may reduce plasma clearance and prolong recovery.
Carcinogenesis, Mutagenesis and Impairment of Fertility: No long-term animal studies of ALFENTA have been performed to evaluate carcinogenic potential. The micronucleus test in female rats and the dominant lethal test in female and male mice revealed that single intravenous doses of ALFENTA as high as 20 mg/kg (approximately 40 times the upper human dose) produced no structural chromosome mutations or induction of dominant lethal mutations. The Ames *Salmonella typhimurium* metabolic activating test also revealed no mutagenic activity.
Pregnancy Category C: ALFENTA has been shown to have an embryocidal effect in rats and rabbits when given in doses 2.5 times the upper human dose for a period of 10 days to over 30 days. These effects could have been due to maternal toxicity (decreased food consumption with increased mortality) following prolonged administration of the drug. No evidence of teratogenic effects has been observed after administration of ALFENTA in rats or rabbits. There are no adequate and well-controlled studies in pregnant women. ALFENTA should be used during pregnancy only if the potential benefit justifies the potential risk to the fetus.
Labor and Delivery: There are insufficient data to support the use of ALFENTA in labor and delivery. Placental

Nursing Mothers: In one study of nine women undergoing post-partum tubal ligation, significant levels of ALFENTA were detected in colostrum four hours after administration of 60 μg/kg of ALFENTA, with no detectable levels present after 28 hours. Caution should be exercised when ALFENTA is administered to a nursing woman.
Pediatric Use: Adequate data to support the use of ALFENTA in children under 12 years of age are not presently available.
ADVERSE REACTIONS: The most common adverse reactions, respiratory depression and skeletal muscle rigidity, are extensions of known pharmacological effects of opioids. See CLINICAL PHARMACOLOGY, WARNINGS and PRECAUTIONS on the management of respiratory depression and skeletal muscle rigidity. Delayed respiratory depression, respiratory arrest, bradycardia, asystole, arrhythmias and hypotension have also been reported. The reported incidences of adverse reactions listed in the following table are derived from controlled and open clinical trials involving 1183 patients, of whom 785 received ALFENTA. The controlled trials involved treatment comparisons with fentanyl, thiopental sodium, enflurane, saline placebo and halothane. Incidences are based on disturbing and nondisturbing adverse reactions reported. The comparative incidence of certain side effects is influenced by the type of use, e.g., chest wall rigidity has a higher reported incidence in clinical trials of alfentanil induction, and by the type of surgery, e.g., nausea and vomiting have a higher incidence in patients undergoing gynecologic surgery.

Percent	ALFENTA (N=785)	Fentanyl (N=243)	Thiopental Sodium (N=66)	Enflurane (N=55)	Halothane (N=18)	Saline Placebo* (N=18)
Gastrointestinal						
Nausea	28	44	14	5	0	22
Vomiting	18	31	11	9	13	17
Cardiovascular						
Bradycardia	14	7	8	0	0	0
Tachycardia	12	12	39	36	31	11
Hypotension	10	8	7	7	0	0
Hypertension	18	13	30	20	6	0
Arrhythmia	2	2	5	4	6	0
Musculoskeletal						
Chest Wall Rigidity	17	12	0	0	0	0
Skeletal Muscle Movements	6	2	6	2	0	0
Respiratory						
Apnea	7	0	0	0	0	0
Postoperative Respiratory Depression	2	2	0	0	0	0
CNS						
Dizziness	3	5	0	0	0	0
Sleepiness/ Postoperative Sedation	2	8	2	0	0	6
Blurred Vision	2	2	0	0	0	0

*From two clinical trials, one involving supplemented balanced barbiturate / nitrous oxide anesthesia and one in healthy volunteers who did not undergo surgery.

In addition, other adverse reactions less frequently reported (1% or less) were: Laryngospasm, bronchospasm, postoperative confusion, headache, shivering, postoperative euphoria, hypercarbia, pain on injection, urticaria, and itching. Some degree of skeletal muscle rigidity should be expected with induction doses of ALFENTA.
DRUG ABUSE AND DEPENDENCE: ALFENTA (alfentanil hydrochloride) is a Schedule II controlled drug substance that can produce drug dependence of the morphine type and therefore has the potential for being abused.
OVERDOSAGE: Overdosage would be manifested by extension of the pharmacological actions of ALFENTA (alfentanil hydrochloride) (see CLINICAL PHARMACOLOGY) as with other potent opioid analgesics. No experience of overdosage with ALFENTA was reported during clinical trials. The intravenous LD_{50} of ALFENTA is 43.0-50.9 mg/kg in rats, 72.2-73.6 mg/kg in mice, 71.8-81.9 mg/kg in guinea pigs and 59.5-87.5 mg/kg in dogs. Intravenous administration of an opioid antagonist such as naloxone should be employed as a specific antidote to manage respiratory depression. The duration of respiratory depression following overdosage with ALFENTA may be longer than the duration of action of the opioid antagonist. Administration of an opioid antagonist should not preclude immediate establishment of a patent airway, administration of oxygen, and assisted or controlled ventilation as indicated for hypoventilation or apnea. If respiratory depression is associated with muscular rigidity, a neuromuscular blocking agent may be required to facilitate assisted or controlled ventilation. Intravenous fluids and vasoactive agents may be required to manage hemodynamic instability.
DOSAGE AND ADMINISTRATION: The dosage of ALFENTA (alfentanil hydrochloride) should be individualized in each patient according to body weight, physical status, underlying pathological condition, use of other drugs, and type and duration of surgical procedure and anesthesia. In obese patients (more than 20% above ideal total body weight), the dosage of ALFENTA should be determined on the basis of lean body weight. The dose of ALFENTA should be reduced in elderly or debilitated patients (see PRECAUTIONS). Vital signs should be monitored routinely. Protect from light. Store at room temperature 15°-30° C (59°-86° F).

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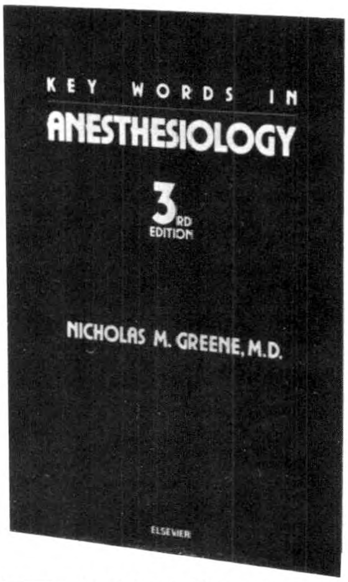

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Editorial

Waking up to Desflurane: The Anesthetic for the '90s?

Edward D. Miller, Jr, MD and Nicholas M. Greene, MD

Key Words: ANESTHETICS, VOLATILE—desflurane

This issue of the Journal contains a report by Jones et al. (1) that describes the first use of desflurane (I-653) in humans. One is prompted to question whether we truly need a new inhalation anesthetic that, at first glance, appears to be quite similar to isoflurane. The introduction of halothane in the late 1950s certainly marked the beginning of an era of new volatile anesthetics with much sought after properties: a total anesthetic allowing high inspired concentrations of oxygen, not irritating when inhaled, nonexplosive, and with minimal side effects. Halothane provided, however, less than complete surgical relaxation, was said to cause rare but potentially lethal hepatitis, and certainly was associated with sensitization of the myocardium to catecholamines, all of which led to the search for other inhalation anesthetics. Fluroxene, methoxyflurane, enflurane, and isoflurane were products of that search. Some of these anesthetics have fallen by the wayside because of their side effects, but others, e.g., enflurane and isoflurane, have become popular to the point of displacing, in some areas, halothane. In the eyes of some, it is with enflurane, and, perhaps even more so, with isoflurane that that new agent, desflurane, must be compared.

As shown in the paper by Jones et al. induction of and emergence from desflurane anesthesia are rapid. This, of course, is not unexpected in view of the low blood/gas partition coefficient (0.424) of desflurane (2). The subjects reported by Jones et al. responded, for example, to commands within 4 min of discontinuing the anesthetic. The minimal alveolar concentration (MAC) of 4.58% in oxygen demonstrates that high inspired oxygen will still be possible. However, a more recent report suggests that the MAC for this agent may be closer to 6.0% in surgical patients (3). Whether the recovery times and "street-ready" times will be significantly shorter in patients anesthetized with desflurane than with other inhalation anesthetics will need closer study. Certainly with today's increased emphasis on outpatient anesthesia, rapid recovery would be advantageous.

Many questions not addressed in this preliminary report need, however, to be resolved before the role of desflurane in the practice of anesthesia can be established. Will desflurane, for example, have effects on blood pressure, heart rate, and other cardiovascular functions similar to those seen with isoflurane? Will the metabolism of desflurane in humans under clinical conditions be similar to that of isoflurane? Will desflurane interact more or less with muscle relaxants than isoflurane? Will desflurane have the potential for causing a "steal phenomenon" involving myocardial blood flow as reported with isoflurane? These and a multitude of other areas will need to be investigated thoroughly before one can say that this new agent is superior to the standard against which, in the eyes of many, it should be measured—isoflurane. But is isoflurane the best standard to use? There are those in the anesthetic community who can argue convincingly that halothane has many advantages in the vast majority of patients because it depresses the cardiac output, decreases myocardial oxygen demand more than it decreases myocardial oxygen supply, and causes little alteration in total peripheral resistance. That debate persists, and cannot be resolved here. One can be assured, however, that the comparison of agents will bolster some academic careers.

Received from the Department of Anesthesiology, Columbia University College of Physicians and Surgeons, New York, New York; and the Department of Anesthesiology, Yale University School of Medicine, New Haven, Connecticut. Accepted for publication September 21, 1989.

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No discussion of a new drug would be complete without some discussion of cost. The fact that the patent on isoflurane is coming to its end requires the manufacturer to develop a new product, e.g., desflurane. Certainly the manufacturer will spend great sums of money to bring desflurane to the marketplace. The cost of the drug will necessarily be priced to offset the research and promotional costs. But for us as practitioners, it is not only the increased cost for this drug as compared with other agents that we must bear in mind but the new technology required to give this agent safely. Because the vapor pressure of I-653 is 664 mm Hg at 20°C (vs 240 mm Hg at 20°C for isoflurane), a pressurized vaporizer with electrically controlled temperature is needed. What does this mean? It means we will need to upgrade our machines and replace vaporizers if we use this new agent. Will the manufacturers bear, at least partially, the increased cost of the equipment needed to administer desflurane, including the vaporizers? If the cost of desflurane is too great, it would become impractical to use.

The relatively high MAC of desflurane means also that large amounts would be vaporized if we continue to use almost routinely and with little rationale high (3–5 L) fresh gas inflows in semicircle anesthesia circuits. To decrease the amount of desflurane used and thus make its use more economical, closed or low-flow systems will be needed. This is not necessarily bad, but more widespread use of equipment to monitor concentrations of anesthetics in ventilatory gases will be necessary and these monitoring devices will further add to the cost. The use of these monitors could, however, improve anesthetic care. The technology to make these measurements has improved dramatically in the last several years and the cost of these devices has decreased. If desflurane were widely adopted, we may change our mode of practice and this could effectively decrease the total cost of anesthetic agents.

Rapid emergence is certainly an attractive feature of desflurane. However, the subjects in the paper by Jones et al. were volunteers, and not surgical patients, and therefore awoke pain-free. After a major surgical procedure, care will have to be taken that the patient is allowed to awaken with some degree of analgesia and the effect of this on the rapidity of emergence is unknown. Certainly the use of the nitrous oxide-narcotic technique with muscle relaxation is appealing because at the end of the procedure the patient is awake and often pain-free. The ability to titrate narcotics during a nitrous oxide-narcotic technique is illustrated by such emergence.

In the final analysis, does this new agent, desflurane, justify the expense and the efforts by the company and the investigators to bring to us an agent that perhaps might be ever so slightly better than other currently available agents? Yes, it does. We should not remain complacent with what we have now. All our anesthetic agents and techniques have faults. We still do not provide the perfect anesthetic for every patient. By bringing new agents to the marketplace we learn more about our older agents. We reinvestigate, we compare, and we see what is good about the old and what is not so good about the new. We must constantly ask for better agents because we do not yet have the ideal anesthetic. Yes, desflurane has advantages. Yes, it also has limitations. Though unlikely to be the ultimate in inhalation anesthetics, desflurane deserves our attention and evaluation as a step along the path to the grail of our quest, the perfect anesthetic.

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Kinetics and Potency of Desflurane (I-653) in Volunteers

R. M. Jones, FCAnaes, J. N. Cashman, FCAnaes, E. I. Eger II, MD, M. C. Damask, MD, and B. H. Johnson, MS

JONES RM, CASHMAN JN, EGER EI II, DAMASK MC, JOHNSON BH. Kinetics and potency of desflurane (I-653) in volunteers. Anesth Analg 1990;70:3–7.

The inhalation anesthetic, desflurane (I-653), is a methyl ethyl ether halogenated entirely with fluorine and differing from isoflurane only in the substitution of fluorine for chlorine on the α-ethyl carbon. Relative to presently used potent inhalation anesthetics, desflurane has low blood/gas (0.42) and oil/gas (18.7) partition coefficients. These indicate that it will undergo rapid washin and washout (and hence rapid induction of and recovery from anesthesia) and have a MAC value of about 5%. In the present study we demonstrate that desflurane possesses these characteristics in healthy young volunteers. After a 10-min exposure to desflurane the ratio of alveolar (F_A) (determined by end-tidal sampling) to inspired (F_I) concentration (F_A/F_I) was 0.82. Washout was similarly rapid; 10 min after discontinuing administration of desflurane, the alveolar concentration relative to the last concentration during administration of anesthetic (F_{AO}) was 0.11 (F_A/F_{AO}). These values are similar to those for nitrous oxide. Volunteers responded to commands an average of 2.7 min after discontinuing anesthetic administration. The values for MAC-awake and MAC (the latter determined by tetanic stimulation of the ulnar nerve using surface electrodes) were 2.42% and 4.58% and the ratio of the former to the latter was 0.53.

Key Words: ANESTHETICS, VOLATILE—desflurane. PHARMACOKINETICS, WASHIN, WASHOUT. POTENCY—MAC, MAC-awake. RECOVERY, ANESTHESIA.

The inhalation anesthetic, desflurane (I-653), is a methyl ethyl ether that differs from isoflurane only in the substitution of fluorine for chlorine on the α-ethyl carbon. Its blood/gas partition coefficient is 0.42 (1), less than that for any other halogenated anesthetics (2–4) and, indeed, less than that for nitrous oxide (N_2O) (partition coefficient 0.46 [5]). Because of the direct relationship between blood solubility and uptake, the rate of rise of alveolar (and thus brain) concentration with respect to inspired concentration should be rapid, like the decrease in alveolar concentration after discontinuing administration of the agent. Thus induction of, and recovery from, anesthesia with desflurane should be more rapid than with other halogenated agents.

However, compared with other agents the oil/gas partition coefficient of desflurane is relatively low (18.7) (1). Because of the direct relationship between oil or lipid solubility and potency (6), the relatively low lipid solubility suggests that potency, measured by the concentration required to cause loss of response to command or to a standard painful stimulus, would be lower than that of other agents (i.e., the MAC value would be higher).

In the present study we have measured, in healthy volunteers, the rate of increase in alveolar (F_A) toward inspired (F_I) concentration (F_A/F_I, washin) for desflurane and the rate of decrease in F_A relative to the alveolar concentration immediately before stopping the administration (F_{AO}) on discontinuing exposure (F_A/F_{AO}, washout). We also determined its potency by defining the concentrations associated with failure to respond to verbal command and to a standard painful stimulus.

Methods

Guy's Hospital Ethical Committee granted permission to study ten volunteers who gave written informed consent. All volunteers were ASA physical

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status I young males. All had normal physical examinations, electrocardiograms, and standard hematologic and biochemical tests. No subject who had smoked during the previous 5 yr or had taken any medication, including over-the-counter medicines, was allowed to enter the study. All were tested before test-drug exposure for the Australia antigen and for illicit drug taking, and all abstained from alcohol or caffeine-containing drinks for at least 24 h before the study.

Before administering desflurane, subjects breathed 100% oxygen (O_2) for 10 min from an anesthetic circuit incorporating a carbon dioxide (CO_2) absorbant. After denitrogenation subjects breathed 1.8% (volunteers 1–5, group 1) or 5.4% (volunteers 6–10, group 2) desflurane from a second anesthetic machine and circle system, identical to the first, but primed with desflurane at one of these two concentrations. The anesthetic was delivered to the circle system from a modified Ohio DM 5000 anesthesia machine with an electrically heated, temperature-controlled pressurized vaporizer.

Inspired (F_I) and end-expired (F_E) desflurane concentrations, as well as end-expired CO_2, were monitored by separate Datex 254 Multigas analyzers. These were calibrated before and after each test-drug run with tank standards of 1.5%, 3.0%, and 6.0% desflurane. The standards were made from gravimetric measurements and a knowledge of the internal volume of the tanks. All concentrations of desflurane were corrected for barometric pressure to the concentration at 1 atm. Carbon dioxide calibration was accomplished with standards supplied by the manufacturer of the analyzer. Volunteers breathed from a clear plastic mask. An adaptor with a side-port permitted the attachment of a catheter that was linked to the gas analyzer. The inspired gas was delivered to the adaptor from the Y connector of the anesthetic circuit via a corrugated Teflon tube and angle piece. The 50-mL deadspace of the tube and angle piece protected the end-tidal sample from contamination with inspired gas. Inspired desflurane was sampled from the inspiritory limb of the circle.

Volunteers spontaneously breathed desflurane in O_2 throughout the test-drug run and no other drugs, including premedicants or N_2O, were administered. Washin of agent was determined in both groups of volunteers by recording F_I and F_E of desflurane, as well as expired CO_2, at 1, 2, 3, 5, 7, 10, 15, 20, 25, and 30 min, during which time the inspired concentration was maintained at the priming level (1.8% group 1, 5.4% group 2) by adjusting vaporizer or diluent flow, or both.

After completion of measurements to determine uptake, the F_I of desflurane was adjusted in a stepwise manner to determine its potency. In group 1, the F_A at which subjects did not respond to verbal command ("squeeze my fingers," "open your eyes," each command repeated forcefully three times) was first determined, and then the F_A at which subjects did not respond to a standard painful stimulus (supramaximal 60-Hz tetanic stimulus applied to the ulnar nerve for a maximum of 30 s) was determined. In group 2 these end-points were determined in the reverse order. In both groups F_I was increased or decreased by 0.8% increments and then held for 15 min so that the highest steady-state concentration at which the subject did respond, and the lowest concentration at which the subject did not respond, could be determined (i.e., the end-points were bracketed). Both end-points (lack of responses to command and painful stimulus) in each subject were recorded as the average of these two bracketed concentrations.

After determining potency, washout of desflurane was determined in all subjects by recording F_E at the same times after discontinuing administration as those recorded during washin. In addition, the time taken to appropriately respond to command was recorded in group 1 volunteers in whom washout was initiated after breathing anesthetic (not sedative) concentrations of desflurane.

Results

All results are reported as mean ± SD. Volunteers were aged 25.6 ± 5.3 yr and were of normal height (180.5 ± 5.9 cm) and weight (76.8 ± 8.5 kg). No change in calibration of the Datex monitors was found on any occasion when comparing calibrations made before and after each study.

Kinetics

The ratios between F_A and F_I are shown in Figure 1 for both groups of volunteers. In group 1 (1.8% inspired) washin was faster in the first 3 min, and thereafter was slower, than in group 2 (5.4% inspired), but the differences did not reach statistical significance. End-tidal equilibration was 90% complete (i.e., $F_A/F_I = 0.9$) by 30 min.

Washout was, like washin, rapid in both groups despite differences in the sequence of concentrations delivered before discontinuing the agent (Figure 2). Washout in group 1 started when F_{AO} values were 3.7%–5.9% after 95 ± 19 min of exposure (i.e., early

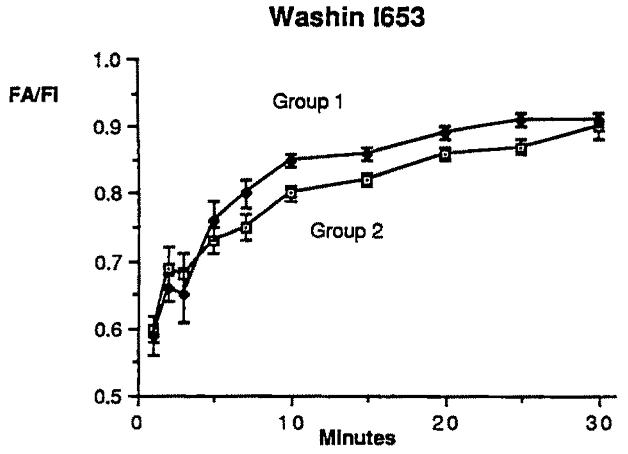

Figure 1. F_A/F_I for desflurane given to ten volunteers increased rapidly whether the inspired concentration (F_I) was 1.8% or 5.4%. In both groups respiration was spontaneous and normal as defined by end-tidal CO_2 levels of 5%–6.5%.

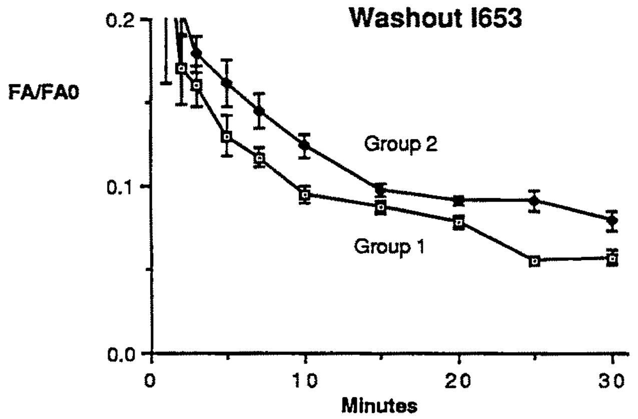

Figure 2. F_A/F_{AO} for desflurane after 1.5 h of anesthesia decreases rapidly and at a rate comparable to that seen with N_2O after a similar period of administration. Except for the values at 20 and 25 min the rate of decrease did not differ significantly in the five subjects in whom the last stable alveolar concentration of desflurane during anesthetic administration (i.e., the F_{AO}) was 2.8% and in the five subjects in whom F_{AO} was 4.3%.

concentrations were less than later ones, and less than the F_{AO} used to define washout). In group 2 washout was undertaken from F_{AO} values of 2.2%–3.3% after 84 ± 14 min of exposure (i.e., early concentrations were greater than later ones, and greater than the F_{AO} used to define washout). As might be anticipated from the sequence used in group 2, the rate of washout in group 2 was slower than was washout in group 1, but only the values at 20 and 25 min were statistically significantly different ($P < 0.05$, ANOVA plus LSD for individual comparisons). The alveolar concentrations decreased by 90% ($F_A/F_{AO} = 0.1$) in both groups after 10–15 min of washout. In group 1 subjects, in whom washout was initiated after breathing anesthetic rather than sedative concentrations of desflurane, response to command and awakening always occurred within 4 min (average 2.7 ± 1.2 min) of discontinuing the anesthetic.

Potency

It was not possible to determine a bracketed steady-state expired concentration (i.e., F_A) that prevented response to command in two subjects (one each in groups 1 and 2) because of the presence of the excitement that can accompany inhalation induction of anesthesia. The values of F_A determined in the other eight subjects averaged 2.42% ± 0.49% desflurane, and this value did not differ significantly if the subjects had previously been exposed to higher anesthetic concentrations (group 2) rather than lower (group 1); the values were 2.30% ± 0.59% in group 1 and 2.54% ± 0.40% in group 2. Similarly, the F_A preventing response to a painful stimulus (a positive response was defined as movement other than movement in the stimulated limb) was not significantly different in groups 1 and 2, the values being 4.60% ± 0.47% and 4.55% ± 0.77%, respectively, and 4.58% ± 0.6% overall. No subject remembered the stimulation applied in the determination of potency.

Discussion

As predicted from its low solubility in blood and tissues, both the washin and the washout of desflurane were rapid. The rate of uptake shown in Figure 1 is similar to that observed with N_2O when administered in trace concentrations (7,8), that is, without the acceleration caused by the concentration effect (9). F_A/F_I after 10 min of administration of desflurane was 0.82. This compares with a value for F_A/F_I of 0.87 after 10-min ventilation with 1.9% N_2O (3) and a value of 0.92 with 4% N_2O (4). Thus, the rate of uptake of desflurane is appreciably more rapid than occurs with less soluble agents such as enflurane or halothane. Comparable values of F_A/F_I after breathing subanesthetic concentrations of these agents for 10 min were 0.42 (halothane) and 0.52 (enflurane) (7).

The concentration effect may provide part of the explanation for the tendency toward a more rapid increase in F_A seen in group 2 volunteers who were given 5.4% inspired desflurane, as opposed to the 1.8% given to group 1. This difference in inspired concentrations would effectively decrease the solubility of desflurane in the second group relative to the first by 4% (10). However, the principal cause for the small difference in the relative rates of washin is probably that volunteers in group 2 were effectively anesthetized, and thus had a lower metabolic rate and cardiac output, whereas the group 1 subjects were not anesthetized (all were able to respond appropriately to command after 30 min of breathing 1.8% desflurane).

The accuracy of our determinations of the kinetics and potency of desflurane depends principally on the accuracy of the sampling and measuring techniques used. To ensure that end-tidal and hence fractional alveolar concentration (F_A) samples were not contaminated by inspired gas, a dead space was incorporated into the delivery system, as described above. The presence of this protective dead space was thought to be a potential source of error in the analysis of inspired (F_I) desflurane, and samples of F_I were thus taken from the inspiratory limb of the circuit. Inspired and expired desflurane were measured by separate gas analyzers, but as a guarantee of the accuracy of the system we were able to check the inspired concentrations at the catheter mount adaptor, and invariably, the concentration sensed by the two analyzers did not differ. This observation also suggests that water vapor did not appreciably dilute the end-tidal samples, and no correction was made for this. Each analyzer was calibrated with identical tank standards immediately before and after each study, and no change in calibration or differences between the analyzers was ever noted.

Although we did not specifically determine the speed of induction of anesthesia with desflurane, all subjects were questioned immediately after the study about their memory for events after the first breath of the agent. No subject in whom anesthesia was induced with 5.4% desflurane remembered anything after the first few breaths. In addition, although all subjects in group 1 responded appropriately to command after breathing 1.8% desflurane for half an hour, most had little memory for events during this period, including memory for the excitement that often accompanies inhalational induction of anesthesia. The time taken to correctly respond to command ("open your eyes," "squeeze my fingers") was specifically recorded in group 1, in whom discontinuation of desflurane was initiated from the anesthetized state as opposed to group 2 volunteers who were given subanesthetic concentrations during the terminal exposure to desflurane. The time to awaken varied from 1 to 4 min (mean 2.7 ± 1.2 min). Thus, the rapid decrease in alveolar concentration after discontinuing administration translates into rapid recovery from anesthesia. This is consistent with the rapid recovery seen with desflurane in rats (11) and pigs (12). The rate at which alveolar desflurane concentration decreases during washout is comparable to that reported by other investigators for N_2O. Ten minutes after discontinuing desflurane administration, F_A/F_{AO} was 0.11 ± 0.02, which compares with F_A/F_{AO} values reported 10 min after discontinuing N_2O of 0.09–0.10 (13–15).

Anesthetic potency is related to fat solubility: the more soluble an agent is, the more potent it is. Using this relationship, plus the known MAC of desflurane in rats (16), dogs (17), rabbits (17), and pigs (12)—together with the relationship of potency in these species to humans (16,17), the predicted MAC in humans should be about 5%. Our results, using tetanic stimulation of the ulnar nerve, found MAC to be 4.58%. Tetanic stimulation has previously been used as a noxious stimulus in the determination of MAC in humans (18) and has been shown to correlate well with the standard noxious stimulus (skin incision) used in patients (19). Both these studies (18,19) used needle electrodes to stimulate the ulnar nerve at the wrist, whereas we used surface electrodes. Thus it is possible that the MAC of desflurane in patients might be a minimum of 4.58% and may be slightly higher.

The anesthetic concentration midway between the value permitting response to command and that just preventing the response has been termed the MAC-awake concentration (20). The value for MAC-awake in the present study, determined at a constant and steady alveolar concentration of desflurane, was 2.42% ± 0.49%. The ratio of MAC-awake to MAC was 0.53, which compares with a figure of 0.52 previously determined for halothane (20). The accuracy of these results is suggested by the following reasoning. Volunteers in groups 1 and 2 in the present study had essentially the same values for MAC and MAC-awake. Had equilibrium not been complete, or had end-tidal sampling been inadequate, the values determined early in anesthesia should have been greater than the values determined later. That they were not suggests that equilibration had taken place and that the sampling technique used was reliable.

In conclusion, predictions made concerning the rapid uptake and washout of desflurane based on its low blood solubility and for potency based on its relatively low fat solubility have been borne out in this trial in healthy, young volunteers. The low blood/gas partition coefficient may be a particular advantage as it allows for rapid induction of, and recovery from, anesthesia and should permit rapid adjustments of anesthetic depth to be made. The lower fat solubility and thus relatively lower potency of desflurane, compared with other halogenated anesthetics, suggests that the agent may be most appropriately delivered with low flow breathing systems, but desflurane is sufficiently potent so that even if administered at 2 MAC concentrations it will allow for the use of high (about 90%) inspired O_2 concentrations.

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Differences in Magnitude and Duration of Opioid-Induced Respiratory Depression and Analgesia with Fentanyl and Sufentanil

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BAILEY PL, STREISAND JB, EAST KA, EAST TD, ISERN S, HANSEN TW, POSTHUMA EFM, ROZENDAAL FW, PACE NL, STANLEY TH. Differences in magnitude and duration of opioid-induced respiratory depression and analgesia with fentanyl and sufentanil. Anesth Analg 1990;70:8–15.

The magnitude and duration of analgesia and respiratory depression induced by fentanyl (1.0, 2.0, and 4.0 μg/kg) and sufentanil (0.1, 0.2, and 0.4 μg/kg) after intravenous administration over 30 s were measured in 30 healthy young adult male volunteers divided into three groups and studied in a double-blind, randomized fashion. Each volunteer received one dose of fentanyl or sufentanil and no sooner than 48 h later, the corresponding equipotent dose of the other opioid. End-tidal CO_2 *and ventilatory and occlusion pressure responses to* CO_2 *rebreathing were used to measure drug-induced respiratory effects. Analgesic effects were assessed by changes in the pain threshold to electric shock applied to the forearm. Plasma levels of fentanyl and sufentanil were measured by radioimmunoassay. Testing and sampling intervals were 5, 30, 60, 90, 120, 240, 300, and 360 min after drug administration.*

The magnitude and duration of depression of the ventilatory and occlusion pressure response were significantly less with sufentanil compared with fentanyl, irrespective of dose. Ventilatory and occlusion pressure responses returned to control values by 30 and 30 min, respectively, after sufentanil and by 240 and 120 min, respectively, after fentanyl. Statistically significant elevations of the pain threshold were, however, greater and longer lasting after sufentanil compared with fentanyl. Pain threshold returned to control values 180 min after sufentanil but only 90 min after fentanyl. These results suggest that sufentanil may provide better patient comfort with less respiratory depression than does fentanyl.

Key Words: ANALGESICS, FENTANYL, SUFENTANIL. PAIN, EXPERIMENTAL—fentanyl, sufentanil. VENTILATION, FENTANYL, SUFENTANIL.

It is often assumed that the severity and duration of respiratory depression induced by opioids parallel the degree of analgesia. This assumption frequently limits the clinical use of opioids as analgesic and anesthetic agents. However, each opioid has different affinities and interactions with the several types of opioid receptors resulting in unique pharmacologic profiles for different opioids (1,2). Furthermore, the subtyping of μ opioid receptors into μ_1 and μ_2 (3) and the evidence that these separate sites are responsible for opioid-induced analgesic (μ_1) and respiratory depressant (μ_2) effects, respectively, cast doubt on the premise that all "pure" μ agonist drugs (e.g., fentanyl and sufentanil) necessarily produce similar degrees of analgesia and respiratory depression.

Fentanyl and its *N*-4 thienyl derivative, sufentanil, are two very potent opioids frequently used in anesthesia. Although both are classified as pure μ agonists, there are significant differences in their potencies (4), receptor affinities (5), lipophilicity (6), pharmacokinetics (7), and ability to eliminate or attenuate hemodynamic (8) and hormonal (9) responses to surgical stimuli. Clark and colleagues (10), for example, suggest that sufentanil-nitrous oxide(N_2O) produces less respiratory depression and

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greater analgesia in general surgical patients in the immediate postoperative period than does fentanyl plus N_2O. The present study was designed to evaluate in detail the magnitude and duration of respiratory and analgesic effects of fentanyl and sufentanil in healthy human adult volunteers.

Methods

The study was approved by the University of Utah Health Sciences Center Institutional Review Board for Human Research. Written and oral informed consent was obtained from 30 healthy nonsmoking young adults (aged 18–35 yr). The subjects were divided into three groups of 10. Each group of 10 volunteers was assigned to receive intravenously one dose of sufentanil on one study day and the corresponding equipotent dose of fentanyl on another day at least 48 h later; within each group five subjects were first given sufentanil and then fentanyl and five subjects received the drugs in the reverse order. We used a potency ratio for sufentanil and fentanyl of 10:1. The three doses evaluated were 0.1, 0.2, and 0.4 μg/kg of sufentanil and 1.0, 2.0, and 4.0 μg/kg of fentanyl, respectively. Drug dosage assignments and order of administration were assigned by a computer-generated, permuted block, restricted randomization allocation table. Both subjects and investigators were masked to drug and drug dose.

Each study session began at 8 AM and subjects fasted for at least 8 h and refrained from aspirin, caffeine, and alcohol for at least 24 h before the study. At the beginning of each session after local anesthesia with 0.2 mL of 1% lidocaine, an intravenous infusion of Ringer's lactate solution was started in a hand or forearm vein and continued throughout the experiment at 50 mL/h.

The respiratory effects of fentanyl and sufentanil were assessed by carbon dioxide (CO_2) challenges. Ventilatory drive was assessed by inducing progressive hyperoxic hypercapnia using a modified Read rebreathing circuit as previously described (11,12). The rebreathing apparatus contained a 7.5-L neoprene rebreathing bag enclosed in a lucite box with a Validyne differential pressure transducer measuring the pressure drop across a Fleisch pneumotachograph at the outlet of the box to measure ventilatory flow. Flow was directed either into the rebreathing bag or through the pneumotachograph by a three-way valve located at the mouth of the box, permitting the subject to breathe directly into the room when not rebreathing CO_2. Inspiratory and expiratory limbs of the circuit were separated by a Collins J-Valve. A solenoid-operated occlusion valve was located at the proximal end of the inspiratory airway. The CO_2 concentration was measured by a LB-2 infrared CO_2 analyzer (Beckman Instruments, Inc., Palo Alto, Calif.), which sampled gas at the mouthpiece at a rate of 200 mL/min and returned it to the central chamber of the Collins valve. Airway occlusion pressure was measured by a Microswitch pressure transducer in the central chamber of the Collins valve. The pressure signal was low-pass-filtered at 30 Hz. Total circuit volume was 9 L. Inspiratory circuit resistance was 1.9 cm $H_2O \cdot L \cdot s^{-1}$. Expiratory circuit resistance was 1.7 cm $H_2O \cdot L \cdot s^{-1}$ and constant between flow rates of 15 and 135 L/min.

Flow, CO_2, and pressure signals were sampled by a microcomputer (Motorola Exorciser II) 12-bit analog to digital (A/D) convertor (Burr-Brown MP7208 Data Acquisition System) with a resolution of 4.8 mV per A/D unit and a range of ±10 V. Occlusion pressure (P_{100}) measurements were made at the start of every inspiration. The inspiratory occlusion valve was closed 300 ms after the start of expiration. If the shape of the occluded pressure waveform was satisfactory, inspiration pressure was sampled and stored. A signal to reopen the valve was sent 120 ms after the onset of inspiration.

Rebreathing Data Collection and Analysis

After allowing each subject to breathe quietly through the mouthpiece with an occluding nose clip in place, the resting PET_{CO_2} was recorded. The three-way valve was then switched to the rebreathing bag previously filled with 7.8% CO_2 and 92.2% oxygen. At this point, subjects were instructed to take three deep (vital capacity) breaths and then breathe normally or as they felt the need to. For each breath, the following data were displayed on a video terminal and stored in computer memory: inspiratory time (T_I) in seconds; breath duration (T_{TOT}) in seconds; fractional inspired concentration of CO_2 ($\%IN_{CO_2}$), and end-tidal CO_2 concentration ($\%ETco_2$); tidal volume (V_T) in liters; minute ventilation (V_E) in liters per minute; inspiratory mouth occlusion pressure at 100 ms (P_{100}); and elapsed time in seconds since start of CO_2 rebreathing. All gas volumes were corrected to body temperature and pressure saturated (BTPS). Subjects were encouraged to rebreathe as long as possible, but could stop at any time; the desired goal was to reach a PET_{CO_2} of 65 mm Hg. The change in PET_{CO_2} during rebreathing was always at least 20 mm Hg.

After completion of each CO_2 challenge, plots of V_E vs PET_{CO_2} and P_{100} vs PET_{CO_2} were displayed on the video display terminal. To ensure that the regression line reflected only data from the linear portion of the ventilatory response, data from the first ten breaths were excluded from analysis. Data from all other breaths were used for least-squares linear regression. The resting PET_{CO_2}, the slope of V_E vs PET_{CO_2}, and the slope of P_{100} vs PET_{CO_2} were saved for later analysis after the study was completed.

Analgesic Effects

Pain threshold and analgesic drug effects were determined using a model S88 stimulator and stimulation isolation unit (Grass Instrument Co., Quincy, Mass.) and a constant current unit (CCU IA; Grass Instrument Co.) to deliver an electrical stimulus (square wave, 60 Hz) of 0.4-s duration through a concentric (Tursky) electrode (Farral Instruments) applied to the dorsal nondominant forearm (12–14). This methodology has been shown to be sensitive to therapeutic (analgesic) doses of morphine (12,14).

The electrode was applied to the skin of the nondominant forearm after shaving the area and preparing it with an abrasive cream. After removing the abrasive cream, electrode contact was insured with a standard conductive gel. Initial current applied was below sensation threshold. After this, the current was increased by 0.2–0.5 mA every 5 s until the subject described the current as painful (pain threshold). Three such measurements were taken and averaged at each test time. Pain thresholds were always determined after CO_2 challenges.

Fentanyl and Sufentanil Plasma Levels

Venous blood samples were analyzed in each drug dosage group by radioimmunoassay in conjunction with Janssen Laboratories by previously described methods (15,16). Sensitivity for fentanyl and sufentanil was continuous down to plasma levels of 0.1 ng/mL.

Testing Intervals

Blood samples for plasma drug concentrations as well as CO_2 rebreathing challenges and pain threshold assessments were obtained immediately before drug administration (control) and 5, 30, 60, 90, 120, 240, 300, and 360 min after drug administration. There were missing values in the data matrix. Equipment failure occasionally prevented performance of CO_2 rebreathing challenges and pain threshold assessments at one or two of the preplanned data collection times in some subjects. Similarly, phlebotomy failed occasionally. Values were not missing as a consequence of the drug assignment or the dose assignment.

Data Analysis

Descriptive statistics of the continuous variables included means and standard errors; for resting PET_{CO_2}, slope of V_E vs PET_{CO_2}, slope of P_{100} vs PET_{CO_2}, and pain threshold current, raw variable values after drug administration were transformed to Δ values (difference from control value) before analysis. Descriptive statistics were calculated using module 1D of BMDP.

The inferential statistic for comparing the effect of drug and dose on the control values of resting PET_{CO_2}, slope of V_E vs PET_{CO_2}, slope of P_{100} vs PET_{CO_2}, and pain threshold current was repeated measurement multivariate analysis of variance (MANOVA). The inferential statistic for comparing the effect of drug, dose, and time on the Δ values (after drug administration) of resting PET_{CO_2}, slope of V_E vs PET_{CO_2}, slope of P_{100} vs PET_{CO_2}, and pain threshold current was also MANOVA. Because of the missing values, a restricted maximum likelihood approach was used (17). The linear model chosen included a regression on dose and time. The analyses were performed iteratively with different structured covariance matrices until the Akaike's Information Criterion was maximized (18). The test statistic was a Wald χ^2 statistic; the type I error was set at 0.05. The statistical software for MANOVA was the 5V module of BMDP.

The inferential statistic for the return to control of resting PET_{CO_2}, slope of V_E vs PET_{CO_2}, slope of P_{100} vs PET_{CO_2}, and pain threshold current was a one-sample *t*-test. The test statistic was a *t*-test statistic; the type I error was set at 0.05. The statistical software for the one-sample *t*-test was the 3D module of BMDP.

Inferential statistics for plasma sufentanil and fentanyl concentrations included linear contrast one-way analysis of variance (ANOVA) for each drug. To simplify the dose vs plasma concentration relationship, ANOVA was performed only for data at 5 and 60 min after drug administration. The test statistic was a Fisher F statistic; the type I error was set at 0.05. The statistical software for the ANOVA was the 7D module of BMDP.

Results

Ventilatory Response to CO_2 (V_E/PET_{CO_2})

Before drug administration, ventilatory drive was not identical at the start of the two study sessions (χ^2 =

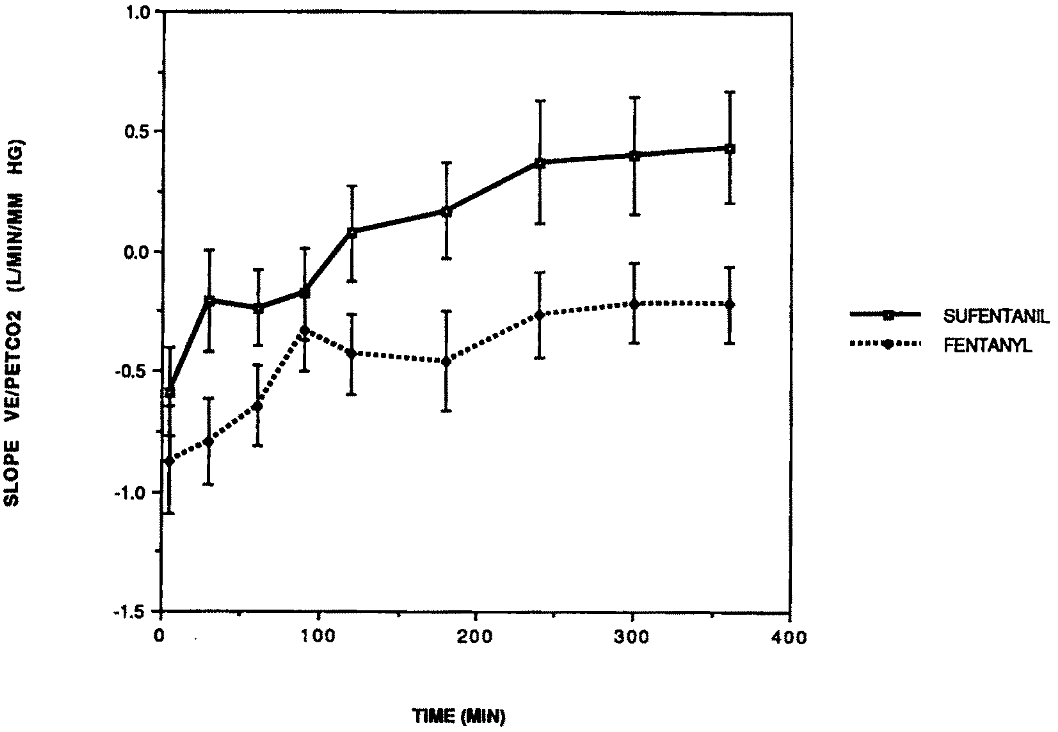

Figure 1. Change over time of the ventilatory response to CO_2 (actual minus control response) after fentanyl and sufentanil (three dosage groups combined for each drug). Control responses are represented as 0.0. The first data points in time are 5 min after drug administration. Fentanyl caused statistically greater and longer-lasting ventilatory depression than sufentanil. Values are mean ± SE.

4.66; df = 1; P = 0.031). After drug administration, the magnitude of ventilatory depression was greater with fentanyl than sufentanil (χ^2 = 11.82; df = 1; P = 0.001; Figure 1). The duration of ventilatory depression was also greater with fentanyl than with sufentanil. Ventilatory drive no longer differed from control values at 30 min for sufentanil (t = −0.98; df = 29; P = 0.335) and at 240 min for fentanyl (t = −0.98; df = 28; P = 0.335). There were no dose-related decreases in the ventilatory response to CO_2 for fentanyl and sufentanil (χ^2 = 0.03; df = 1; P = 0.874).

Occlusion Pressure Response to CO_2 ($P_{100}/P_{ET_{CO_2}}$)

Before drug administration, the occlusion pressure response was also not identical at the start of the two study sessions (χ^2 = 7.15; df = 1; P = 0.008). After drug administration, the magnitude of occlusion pressure response depression was greater with fentanyl than sufentanil (χ^2 = 5.57; df = 1; P = 0.008; Figure 2). The duration of occlusion pressure response depression was also greater with fentanyl than with sufentanil. Occlusion pressure was no longer different from control values at 30 min for sufentanil (t = −1.20; df = 28; P = 0.241) and at 120 min for fentanyl (t = −1.77; df = 27; P = 0.087). There were no dose-related decreases in the occlusion pressure response to CO_2 for fentanyl and sufentanil (χ^2 = 1.42; df = 1; P = 0.233).

Resting End-Tidal CO_2

There were no statistically significant differences between fentanyl and sufentanil with regard to either control values or the magnitude and duration of changes in the resting end-tidal CO_2 (Figure 3).

Pain Threshold

Before drug administration, there was no difference in baseline values between the sufentanil and fentanyl study sessions (χ^2 = 1.15; df = 1; P = 0.285). After drug administration, the magnitude of increase in pain threshold current (analgesia) was greater with sufentanil than fentanyl (χ^2 = 7.21; df = 1; P = 0.007; Figure 4). The duration of effect (increased pain threshold) was also greater with sufentanil than with fentanyl. The pain threshold was no longer different from control values at 180 min for sufentanil (t = 1.89; df = 29; P = 0.069) and at 90 min for fentanyl (t = 1.46; df = 29; P = 0.155). There was no dose-related changes in pain threshold current for fentanyl and sufentanil (χ^2 = 0.50; df = 1; P = 0.480).

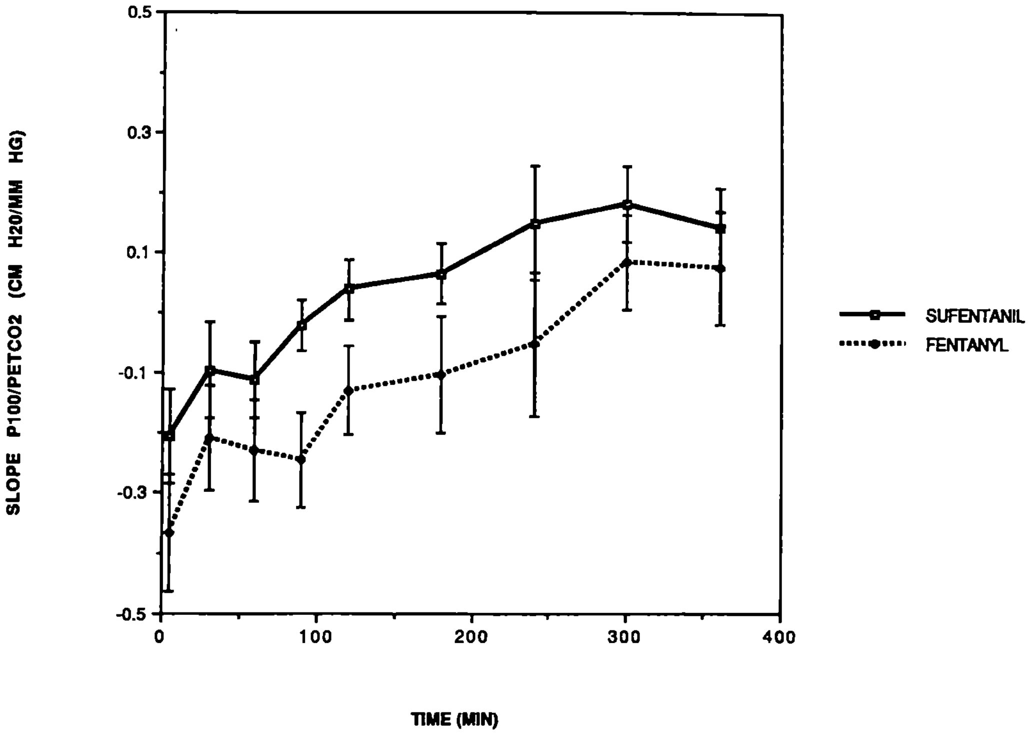

Figure 2. Change over time of the occlusion pressure response to CO_2 (actual minus control response) after fentanyl and sufentanil (three dosage groups combined for each drug). Control responses are represented as 0.0. The first data points in time are 5 min after drug administration. Fentanyl caused statistically greater and longer-lasting depression of the occlusion pressure response than sufentanil. Values are mean ± SE.

Plasma Levels

Increasing doses of fentanyl produced statistically greater mean plasma concentrations of fentanyl 5 min after drug injection [$F_{(1,22)} = 8.48$; $P = 0.0086$; (Table 1)]. Sixty minutes after injection mean plasma levels were <1.0 ng/ml for all three doses of fentanyl and were statistically indistinguishable. Increasing doses of sufentanil also produced increasing mean plasma concentrations 5 min after drug injection [$F_{(1,23)} = 5.70$; $P = 0.0264$; (Table 2)]. Sixty minutes after drug injection no statistically significant dose effect for sufentanil was found.

Discussion

The results of this study demonstrate that sufentanil produces less depression of ventilatory drive but greater and longer lasting analgesia than fentanyl. Our data do not indicate the mechanism(s) for these differences but other investigators have reported similar findings. In addition, several theoretical considerations may explain these results.

Pharmacokinetic comparisons of fentanyl and sufentanil by a number of investigators demonstrate that the latter has a smaller volume of distribution and shorter elimination half-life than the former and that this should be associated with a faster recovery with sufentanil than with fentanyl (7). Sanford and coworkers (19) reported that respiratory depression from "equi-anesthetic" doses of sufentanil did not last as long as did that produced by fentanyl after cardiac surgery, but no evaluation of analgesia was attempted in their study. Although other investigators (8,20) do not confirm Sanford's findings, dosing methods and anesthetic techniques may have obscured differences between fentanyl and sufentanil. In addition, Clark and coworkers (10) found that, when combined with N_2O, fentanyl, administered in a 7:1 ratio to sufentanil, was not only associated with more respiratory depression in the immediate postoperative period but produced less analgesia than sufentanil.

Sufentanil differs in several important ways from fentanyl. It is more lipophilic than fentanyl (7) (*N*-octanol/water partition coefficient 1754 vs 816) and has a greater affinity for opiate receptors (5). This is in agreement with the principle that affinity correlates with potency (21). Stahl et al. (5), in their study of receptor affinity and pharmacologic potency of a series of narcotic analgesics, found sufentanil to have an affinity 12 and 27 times greater than fentanyl

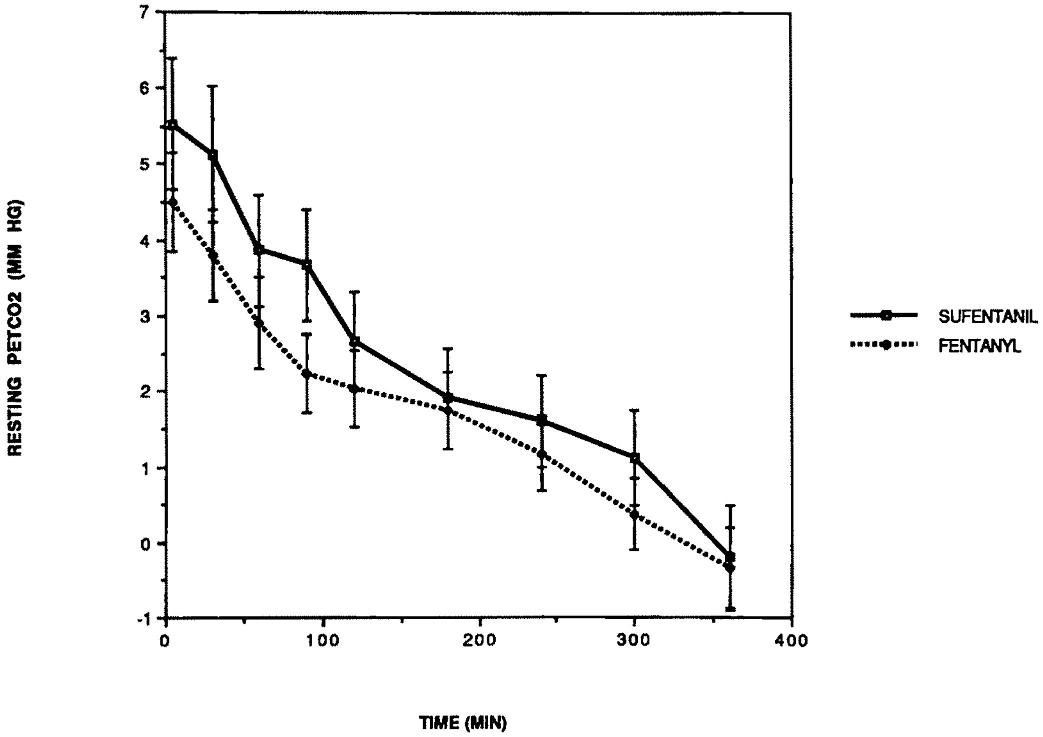

Figure 3. Change over time in the resting end-tidal sufentanil (actual minus control) after fentanyl and sufentanil (three dosage groups combined for each drug). Control responses are represented as 0.0. The first data points in time are 5 min after drug administration. No statistically significant difference was found between the two drugs. Values are mean ± SE.

(depending on the amount of salt present in the assay). In addition, the ED_{50} for inhibition of the rat tail withdrawal reflex to warm water (analgesic measurement) is 19 times less than fentanyl (5). Therefore, although potency ratios for sufentanil to fentanyl are most often quoted as 7:1 with a range of 5:1 to 10:1 (22), the analgesic potency ratio may actually be higher than the potency ratio for other properties such as respiratory depression. Supporting this are the findings of Ling et al. (23) that the duration of morphine-induced analgesia exceeds respiratory depression in the rat. Kalenda and Scheijgrond (24) also reported greater analgesia with sufentanil than fentanyl in the presence of similar degrees of respiratory depression.

There is an accumulating body of evidence that provides a framework for separating opioid-induced analgesia and respiratory depression at the receptor level. According to Pasternak and Wood (25), the μ receptor, the principal site of action of "anesthetic" opioids, has two subtypes (μ_1 and μ_2). The μ_1 sites are high-affinity sites that bind both enkephalins and morphinelike compounds and predominate in areas of the central nervous system known to play major roles in antinociception such as the periaqueductal gray area (25). The μ_2 receptors are low-affinity binding sites that selectively bind morphinelike drugs and play a greater role in opioid-induced respiratory depression (25). The fact that naloxonazine (a relative μ_1 antagonist) reverses the analgesic effects of morphine without significantly altering respiratory depression supports this theory (23). Drugs with higher affinities for μ receptors may, at certain concentrations, bind μ_1 sites preferentially. Non-opiate receptor-mediated mechanisms may, however, contribute to opioid effects, and include increased potassium conductance, voltage-sensitive calcium channel blockade, γ-aminobutyric acid receptor actions, and serotonergic effects (26,27). Whether or not differential binding of sufentanil or fentanyl to μ_1 or μ_2 sites or any of the other above-mentioned mechanisms underlies the differences in the duration of analgesic and respiratory depressant effects we found in this study is not known.

A possible criticism of our study design may be that the assumed potency ratio for sufentanil to fentanyl of 10:1 used to choose doses was too large and accounted for the difference in respiratory depression we found. However, as discussed above, evidence exists in both animals and humans to support this potency ratio or an even greater ratio with regards to analgesia (5,20). In addition, using a lower ratio of perhaps 7:1 would probably have made the magnitude and duration of sufentanil-induced anal-

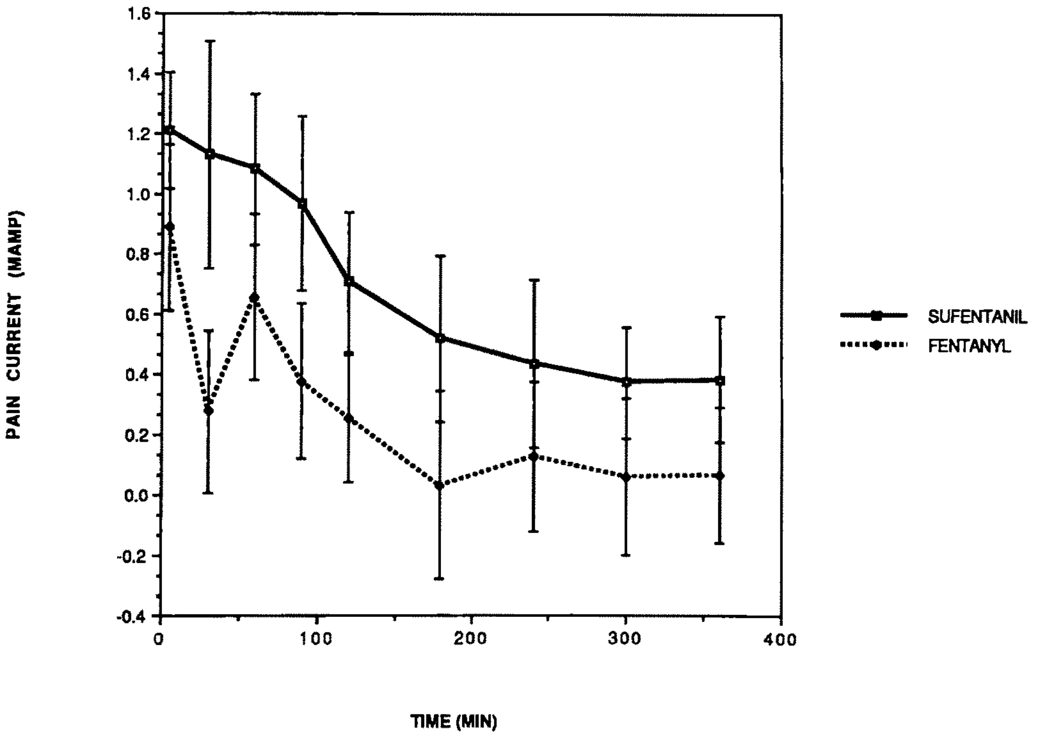

Figure 4. Change over time in the pain threshold current (actual minus control values) after fentanyl and sufentanil (three dosage groups combined for each drug). Control responses are represented as 0.0. The first data points in time are 5 min after drug administration. Sufentanil produced statistically greater and longer-lasting increases in the pain threshold current than fentanyl. Values are mean ± SE.

Table 1. Fentanyl Plasma Levels 5 and 60 min After Injection of Three Doses

Dose (μg/kg)	*n*	5 min (ng/mL)	*n*	60 min (ng/mL)
1	6	3.18 ± 0.87	6	0.52 ± 0.11
2	9	4.27 ± 0.71	9	0.28 ± 0.05
4	9	6.43 ± 0.73	10	0.74 ± 0.12

Values given as mean ± SEM.

Table 2. Sufentanil Plasma Levels 5 and 60 min After Injection of Three Doses

Dose (μg/kg)	*n*	5 min (ng/mL)	*n*	60 min (ng/mL)
0.1	7	0.54 ± 0.27	1	0.50
0.2	8	0.69 ± 0.11	4	0.15 ± 0.03
0.4	9	1.19 ± 0.20	7	0.14 ± 0.03

Values given as mean ± SEM.

gesia even greater than fentanyl while perhaps rendering the magnitude and duration of significant respiratory depression for sufentanil equal to that associated with fentanyl. Thus the implications of our findings would have been essentially unchanged.

Several other observations deserve mention. First, the variability in the different responses we followed was quite large and often limited our ability to detect statistically significant differences among the three dosage groups. Several causes of variability exist. Narcotics, given on a weight basis or titrated to effect, may be associated with as much as fivefold differences in plasma levels (28). Although we found dose-dependent effects on plasma drug levels with both fentanyl and sufentanil, plasma levels do not necessarily correlate with brain and site of action drug concentrations. In addition, the ventilatory response to CO_2 covers a wide spectrum and the normal range of ventilatory responses varies more than 15-fold (0.5–8.0 $L \cdot min^{-1} \cdot mm\ Hg^{-1}$) (29). Apparent differences are thus sometimes difficult to prove to be of statistical significance. Finally, the testing of pain thresholds and the drawing of blood samples may have stimulated our volunteers and thus introduced more variability, and possibly obscured real differences that may have become evident in a more simply designed protocol. Nevertheless, all subjects were tested under identical circumstances and any such possible effects should have been evenly distributed.

Another interesting observation was the overshoot or enhancement of both the ventilatory and occlusion pressure response to CO_2 that occurred 4–6 h after drug injection in the sufentanil but not in the fentanyl group (Figures 1 and 2). The significance, if any, of this finding is uncertain. However, acute tolerance to opioid narcotics can occur within hours (22,30) and as the size of the narcotic dose affects the development of tolerance (31), so may the potency. Tolerance to and withdrawal from opioids have most often been described as affecting the cardiovascular system (31), but these phenomena also affect respiratory drive.

In summary, our results suggest that sufentanil, in doses that produce less and shorter-lasting respiratory depression than fentanyl, produces greater and longer-lasting analgesia than fentanyl. Sufentanil may be preferable to fentanyl in terms of patient comfort and safety.

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1990;70:16–21

Pharmacodynamics and Pharmacokinetics of Epidural Ropivacaine in Humans

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KATZ JA, BRIDENBAUGH PO, KNARR DC, HELTON SH, DENSON DD. Pharmacodynamics and pharmacokinetics of epidural ropivacaine in humans. Anesth Analg 1990;70:16–21.

The purpose of this study was to characterize the pharmacodynamics and pharmacokinetics of three concentrations of the new long-acting amide local anesthetic, ropivacaine, given epidurally in 15 physical status ASA I or II patients for elective lower-extremity orthopedic procedures using a nonrandomized open-label design. Three groups of five patients each received either 0.5%, 0.75%, or 1.0% ropivacaine. Upper and lower levels of analgesia to pinprick were determined at frequent intervals until normal sensation had completely returned. Motor blockade was assessed by use of a modified Bromage scale after each determination of level of analgesia. Fifteen venous blood samples were collected over 12 h after ropivacaine injection. Pharmacokinetic parameters were derived using serum concentration-time data. No significant differences were found between the three groups in terms of onset or recovery of motor and sensory blockade. Median maximum thoracic levels of analgesia achieved were 8, 6, and 5 for the 0.5%, 0.75%, and 1.0% groups, respectively, and occurred at 29 ± 11, 37 ± 21, and 30 ± 9 min. Respective times to two-segment regression were 2.8 ± 1.0, 3.0 ± 0.5, and 2.9 ± 0.6 h. Total durations of sensory blockade were 5.4 ± 0.7, 6.5 ± 0.4, and 6.8 ± 0.8 h, respectively. No statistically significant differences were noted between the three groups in terms of clearance (CL). The mean residence time (MRT) was significantly longer for the 0.5% group when compared with the 1% group. The peak concentration (C_{max}) for the 0.5% group was found to be significantly lower than for either the 0.75% or 1% groups. Mean (± SD) values of the pharmacokinetic parameters for the 0.5%, 0.75%, and 1.0% groups were, respectively, MRT: 9.9 ± 3.6, 7.5 ± 2.6, and 4.5 ± 0.8 h; CL: 0.35 ± 0.21, 0.34 ± 0.24, and 0.52 ± 0.11 $L \cdot kg^{-1} \cdot h^{-1}$; C_{max}: 0.53 ± 0.19, 1.07 ± 0.57, and 1.53 ± 0.60 $\mu g/mL$; and t_{max}: 1.6 ± 1.4, 0.66 ± 0.19, and 0.65 ± 0.16 h. Pharmacokinetic and pharmacodynamic characteristics of epidural ropivacaine are similar to those of epidural bupivacaine in humans.

Key Words: ANESTHETICS, LOCAL—ropivacaine. PHARMACOKINETICS, ROPIVACAINE.

Ropivacaine is a new amide local anesthetic that is a cogener of mepivacaine and bupivacaine. Unlike both mepivacaine and bupivacaine, which are racemic mixtures, ropivacaine is exclusively the S(−) enantiomer (1). Early in vitro and in vivo laboratory studies demonstrated a duration of sensory blockade with ropivacaine similar to or greater than that with bupivacaine (2,3). Recent studies in animals also showed ropivacaine to be similar to bupivacaine in terms of potency of motor blockade (4,5). Although the pharmacokinetic profile for ropivacaine after epidural administration is similar to that of bupivacaine, after intravenous administration in dogs clearance of ropivacaine is more rapid than clearance of bupivacaine (6). Perhaps more significant, however, are other in vitro and in vivo animal studies suggesting that ropivacaine is less cardiotoxic than bupivacaine (1,7–9).

This study examines the neural blockade characteristics (pharmacodynamics) and pharmacokinetics of equal volumes of three concentrations of ropivacaine after epidural administration in humans.

Methods

Fifteen ASA physical status I or II patients entered into a nonrandomized open-label study of ropiv-

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acaine that had been approved by the Institutional Review Board. All patients were scheduled for elective orthopedic procedures having to do with the lower extremities and had consented to epidural anesthesia. Male and female patients aged 22–60 yr, weighing 63–114 kg, and having no clinically significant findings on electrocardiogram or standard blood tests were included in the study. Excluded were patients with a history of sensitivity to local anesthetics; patients with a history of neurological, cardiopulmonary, or psychiatric disease; patients with a history of substance abuse; and women of childbearing potential.

Premedication consisted of 10 mg of diazepam orally 30–90 min before surgery and/or 1–3 mg of midazolam intravenously immediately before injection of the epidural anesthetic. All patients received at least 500 mL of crystalloid solution intravenously before epidural blockade. Patients were placed in the left lateral decubitus position, and the epidural space was identified by a loss of resistance technique using a 17-gauge Tuohy needle via the midline approach at either the L3-4 or L4-5 interspace. A test dose of 3 mL of 1.5% lidocaine with 1:200,000 epinephrine was injected, followed 4 min later by 20 mL of ropivacaine injected over 2 min. Three groups of five patients each received either 0.5%, 0.75%, or 1% ropivacaine. After administration of ropivacaine, patients were immediately put in the supine, horizontal position. Upper and lower levels of analgesia were determined bilaterally using the blunt end of a Sherwood B400 27-gauge short bevel needle at 2, 5, 10, 15, 20, 25, and 30 min, and every 15 min thereafter until normal sensation had completely returned (when surgical conditions permitted sufficient access to the patient). Motor blockade was simultaneously measured by use of a modified Bromage scale (for each leg: 3 = unable to flex hip, knee, or ankle; 2 = able to dorsiflex ankle only; 1 = able to flex knee and ankle; and 0 = able to raise extended leg off bed—scores for each leg were added to give a possible maximum score of 6). Heart rate and blood pressure were measured immediately before blockade and at intervals not exceeding 2, 5, 10, 20, 25, 30, 45, and 60 min, and then every 30 min until 3 h after injection. Patients were seen the day after surgery to determine the presence of residual blockade. Routine electrocardiogram and blood chemistries were repeated on the first postoperative day for comparison with preoperative values.

For pharmacokinetic studies, blood was obtained through a 16-gauge cannula placed in the antecubital vein. Five-milliliter samples were obtained before epidural blockade and at 5, 10, 15, 20, 25, 30, 45, 60, and 90 min, and then at 2, 3, 4, 6, 9, and 12 h after completion of the injection of ropivacaine. Serum concentrations of ropivacaine were determined by gas chromatography using a modification of the method of Coyle and Denson (10). Pharmacokinetic symbols as suggested by Allen et al. (11) are defined in Table 1. Observed times to peak concentrations (t_{max}) and observed peak plasma concentrations (C_{max}) were taken from the serum concentration–time data for each patient. The slope of the terminal phase of the serum concentration–time data was determined for unweighted data using an iterative nonlinear procedure (PC NONLIN) (12). Area under the serum concentration–time curve (AUC) and area under the first statistical moment curve (AUMC) were calculated using the linear trapezoidal rule (13).

Table 1. Definition of Pharmacokinetic Symbols[a]

Symbol	Definition
AUC	Area under the blood concentration–time curve from time zero to infinity ($\mu g \cdot mL^{-1} \cdot h$)
AUMC	Area under the first statistical moment curve from time zero to infinity ($\mu g \cdot mL^{-1} \cdot h^2$)
CL	Total plasma clearance ($L \cdot kg^{-1} \cdot h^{-1}$). Estimated as Dose/AUC
C_{max}	Observed peak concentration from individual serum concentration–time profile (μg/mL)
MRT	Mean residence time of ropivacaine in the body. Estimated as AUMC/AUC
t_{max}	Time to achieve observed C_{max} (h)

[a] As suggested by Allen et al. (11).

Statistical Analysis

Interval data are presented as mean ± SD. Ordinal data are presented as median (range). Intergroup comparisons were accomplished using either a parametric or nonparametric one-way analysis of variance followed by a post hoc test for multiple comparisons as appropriate. For all statistical tests performed, a *P*-value of less than 0.05 was considered to be the minimum level of statistical significance.

Results

No significant intergroup differences in demographic data were noted (Table 2). No adverse reactions to ropivacaine occurred in this study. There were no clinically significant changes in any of the routine laboratory values or electrocardiograms between the preoperative and postoperative measurements.

Two of the 15 patients required supplemental general anesthesia, one in the 0.5% group and one in the 0.75% group. Only the patient in the 0.5% group

Table 2. Demographic Data[a]

Concentration of ropivacaine injected[b]	Age (yr)	Weight (kg)	Height (cm)	Sex (M/F)
0.5%	37 (16)	75 (18)	174 (12)	3/2
0.75%	40 (16)	81 (10)	171 (12)	3/2
1.0%	30 (6)	67 (8)	176 (11)	4/1

[a] Mean (SD)
[b] n = 5 in each group.

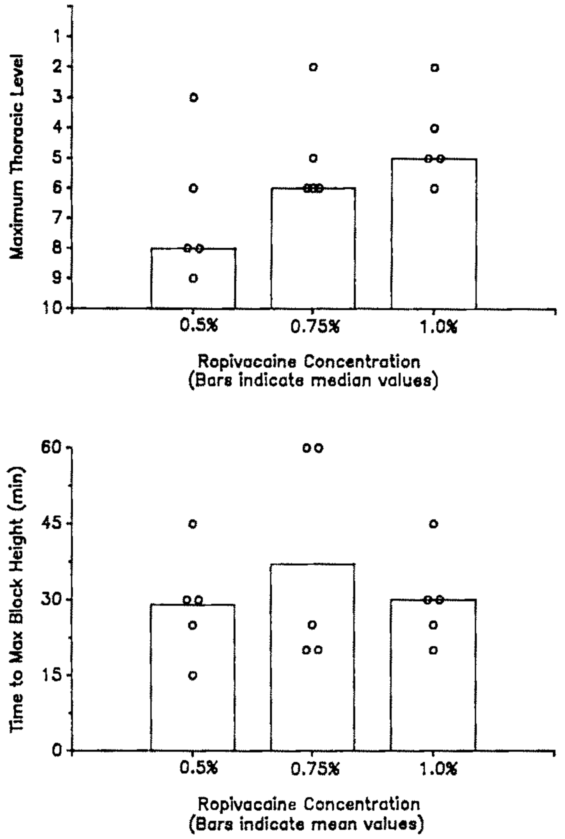

Figure 1. Data from each patient (*circles*) and group means and medians (*bars*) indicating the highest level of analgesia (*top*) and the time to achieve the highest level (*bottom*).

was believed to be a failure of the local anesthetic. Good analgesia into the thoracic dermatomes was demonstrable bilaterally but the patient still had pain with manipulation of the leg, indicating that the block was not complete enough for surgical anesthesia. The patient in the 0.75% group had good surgical anesthesia for 3 h but then experienced pain before the completion of surgery.

No statistically significant intergroup differences were noted for any of the parameters measured. Pharmacodynamic data are summarized in Figures 1–3.

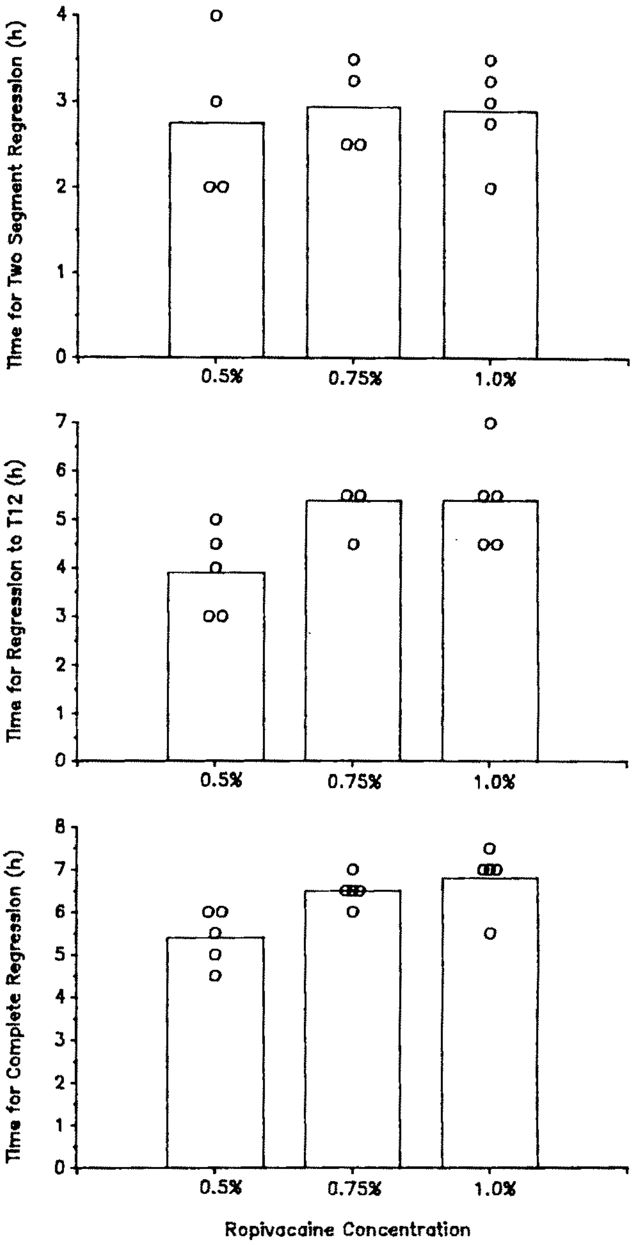

Figure 2. Data from each patient (*circles*) and group means (*bars*) indicating the time from injection of ropivacaine to two-segment regression of block (*top*), return of sensation at T-12 (*middle*), and return of normal sensation in all dermatomes (*bottom*).

Serum concentration–time data are shown for all subjects in Figure 4. No statistically significant intergroup differences were noted for clearance (CL) or t_{max}. Only mean residence time (MRT) and C_{max} for the 0.5% group demonstrated any significant differences from those determined for subjects in the 0.75% and 1.0% groups. Pharmacokinetic data are summarized in Table 3.

Discussion

Few studies have been reported with bupivacaine that are comparable in design to the present study of

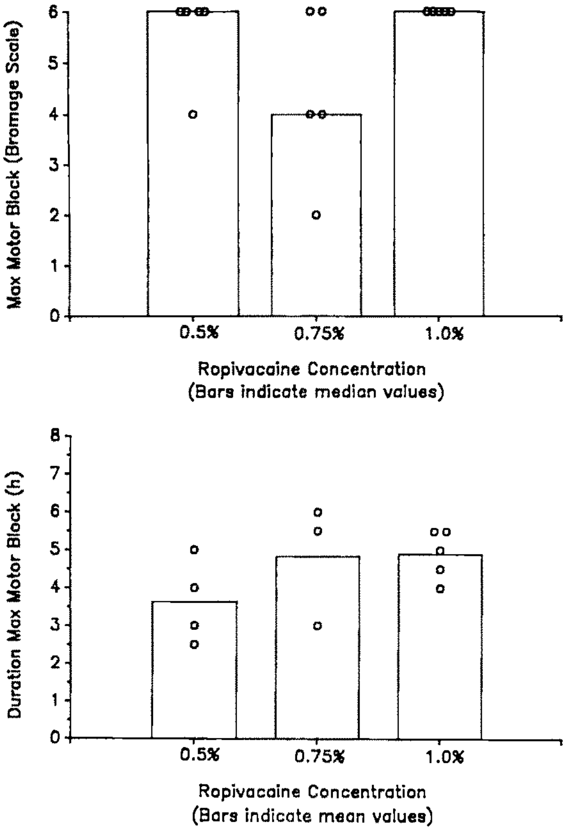

Figure 3. Data from each patient (*circles*) and group means and medians (*bars*) indicating the maximum motor block achieved (*top*); and the time from injection of ropivacaine to return of normal motor function (*bottom*). See text for definition of scale.

ropivacaine. Most studies of single-dose epidural bupivacaine in healthy nonpregnant subjects utilized doses different from this study or included epinephrine in the local anesthetic mixture. Veering et al. (14), in a study examining the effects of age on bupivacaine pharmacokinetics and pharmacodynamics, gave 2 mL of 0.5% bupivacaine with 1:200,000 epinephrine followed by 17 mL of 0.5% plain bupivacaine into the epidural space at L3–4 in 30 patients aged 21–84 yr. These investigators reported the anesthetic effect of bupivacaine to be similar to that obtained with ropivacaine in the present study. For example, in the study by Veering et al. (14) the mean highest sensory level to pinprick achieved within 24 min was T-8, mean time to two-segment regression was 140 min, mean time to recovery of sensation at T-12 was 187 min, and mean time to complete sensory recovery was 400 min. Veering and her coworkers also reported a motor blockade similar to that observed in the present study with a mean motor block score of 4 and a mean duration of 276 min. In terms of pharmacokinetic parameters after epidural administration, bupivacaine in Veering's study had a similar CL (20–30 L/h) when compared with ropivacaine in the present study. Estimates of CL in the present study presume that ropivacaine is completely absorbed after epidural administration (i.e., bioavailability is 1). This hypothesis is based on previous reports with lidocaine, bupivacaine, and ropivacaine in monkeys and with lidocaine and bupivacaine in humans, which showed complete absorption after epidural administration (15–18). An absolute comparison of CL values between bupivacaine and ropivacaine must await the determination of absolute bioavailability of ropivacaine in humans. After epidural injection, 0.5% bupivacaine resulted in serum concentrations (14) similar to those when 0.5% ropivacaine was injected in our present study. The maximum concentrations occurred slightly earlier (18 min)

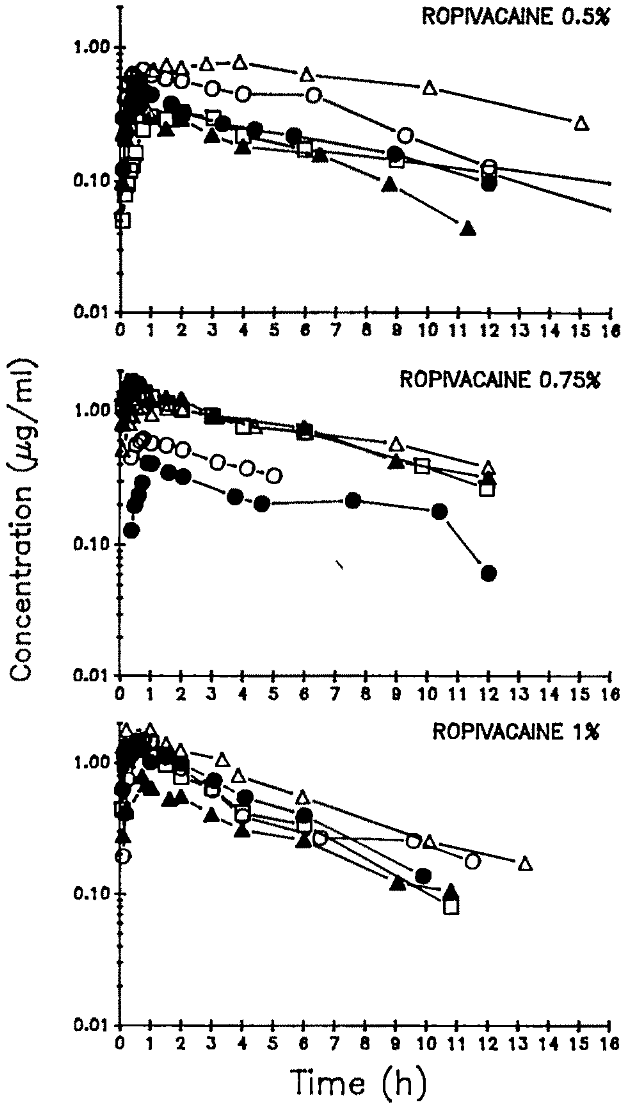

Figure 4. Serum concentration–time data from each patient after epidural injection of 20 mL of either 0.5%, 0.75%, or 1.0% ropivacaine.

Table 3. Individual Pharmacokinetic Parameters[a]

Patient	Weight (kg)	AUC (μg·mL^{-1}·h)	AUMC (μg·mL^{-1}·h^2)	MRT (h)	CL (L·kg^{-1}·h^{-1})	t_{max} (h)	C_{max} (μg/mL)
0.5% Ropivacaine							
1	107	5.96	49.47	8.30	0.16	0.75	0.68
2	64	3.78	36.75	9.72	0.41	0.59	0.50
3	68	13.04	206.73	15.85	0.11	3.90	0.78
4	75	2.21	13.73	6.23	0.60	0.75	0.39
5	63	3.26	30.98	9.50	0.49	2.0	0.32
Mean	75	5.65	67.50	9.92[b]	0.35	1.60	0.53[c]
SD	18	4.35	78.90	3.59	0.21	1.40	0.19
0.75% Ropivacaine							
6	66	3.84	21.43	5.58	0.59	0.75	0.62
7	88	2.78	16.26	5.86	0.61	0.88	0.41
8	92	13.08	156.05	11.93	0.13	0.75	1.06
9	80	11.26	83.69	7.43	0.17	0.42	1.68
10	77	10.16	69.37	6.83	0.22	0.50	1.59
Mean	81	8.22	69.36	7.53	0.34	0.66	1.07
SD	10	4.62	56.65	2.57	0.24	0.19	0.57
1.0% Ropivacaine							
11	64	5.92	25.68	4.34	0.53	0.78	1.49
12	66	6.21	25.43	4.10	0.49	0.58	1.45
13	56	9.65	44.05	4.56	0.37	0.42	2.46
14	77	3.83	22.12	5.77	0.68	0.78	0.79
15	70	5.38	19.24	3.58	0.53	0.75	1.43
Mean	67	6.20	27.30	4.47	0.52	0.65	1.53
SD	8	2.14	9.73	0.81	0.11	0.16	0.60

[a] See Table 1 for expansion of abbreviations.
[b] $P < 0.05$ when compared with the 1.0% ropivacaine group.
[c] $P < 0.05$ when compared with either the 0.75% or the 1.0% ropivacaine group.

with bupivacaine (14) than with ropivacaine (present data).

The lack of statistically significant differences between the motor blocking effects of 0.5%, 0.75%, and 1.0% ropivacaine in the present study has been previously reported in both rat and primate studies (4,5). In dogs, the frequency of motor block was 47% in animals given 0.5% ropivacaine, 96% in those given 0.75%, and 100% in those given 1.0% (4). This is similar to the findings in primates, which showed a trend toward a plateau of the maximum effect with increasing doses (i.e., 0.75% vs 1.0%) (5). The present study also showed a trend toward a maximum anesthetic effect of ropivacaine at concentrations of 0.75% or more. Although, given the small sample sizes, no statistically significant intergroup differences could be demonstrated for duration of sensory blockade, there appeared to be a trend showing 0.5% ropivacaine to have shorter times to both two-segment regression and complete sensory recovery. There was no correlation between motor blockade data and dose of ropivacaine. Based on the data from this study, it appears that 20 mL of 0.5% ropivacaine is not as reliably effective as 20 mL of either 0.75% or 1.0% ropivacaine. The present study evaluated only the effects of a change in concentration with constant volume (and hence a change in total dose); no analysis of a change in volume at a constant dose was made. Our findings are consistent with the data of Thompson et al. (19), who reported the duration of sensory block for 0.5%, 0.75%, and 1.0% ropivacaine to be 5.75, 8.1, and 7.6 h, respectively. No statistically significant intergroup differences were demonstrated (19). A similar study in humans by Concepcion et al. (20) using 20 mL of 0.5%, 0.75%, and 1.0% epidural ropivacaine showed less difference in block duration between the three concentrations than those noted in either the present study or in the study by Thompson et al. (19). Concepcion et al. (20) reported times to two-segment regression of 2.75, 2.73, and 2.63 h and for complete sensory recovery 6.3, 6.6, and 7.3 h for 0.5%, 0.75%, and 1.0% ropivacaine, respectively. In contrast to these data, patients given ropivacaine for brachial plexus blockade developed profound motor and sensory blockade with a ropivacaine concentration of 0.5% (21).

The apparent decrease in MRT observed with increasing the concentration of ropivacaine is likely due to the prolonged t_{max} noted for two patients in the 0.5% group. Absolute bioavailability studies in primates have shown ropivacaine to exhibit a biphasic absorption pattern (i.e., a fast absorption phase followed by a slow phase similar to other local anesthetics in humans [17,18]). It is possible that this slow phase is of primary importance in these two patients. Although statistically significant, it is unlikely that this will ever prove to be clinically significant.

As expected, C_{max} increased with increasing dose. It is likely that C_{max} in the 1.0% group was not significantly increased over the 0.75% group because of the extremely small sample size. Increasing the group size to 12 subjects would give an 80% power of detecting a 43% increase with a coefficient of variation of 40%.

A recent study by Lee et al. (22) determined pharmacokinetic parameters for ropivacaine after an intravenous infusion in healthy male volunteers. Lee et al. reported a higher CL (43.2 ± 9.6 L/h) than in the present study. This result is not unexpected, as the CLs for lidocaine and bupivacaine after epidural administration are also lower than the corresponding values for these drugs after intravenous administration (15,16,18). In addition, a similar finding has been reported for ropivacaine in monkeys (17). This decrease in apparent CL after epidural administration is thought to be due to the biphasic absorption profile exhibited by lidocaine and bupivacaine, which causes slow drug absorption to continue well into the terminal disposition phase (18).

In summary, epidural ropivacaine at concentrations of 0.5%, 0.75%, and 1.0% provided adequate anesthesia for orthopedic lower-extremity procedures in 15 healthy patients. Pharmacodynamic and pharmacokinetic characteristics of ropivacaine are similar to those of bupivacaine, making ropivacaine a potential alternative agent to bupivacaine, one that would be more clinically attractive if toxicity studies show ropivacaine to be a safer medication.

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Fatty Acid Lessens Halothane's Inhibition of Energy Metabolism in Isolated Hepatocytes

Gerald L. Becker, MD

BECKER GL. Fatty acid lessens halothane's inhibition of energy metabolism in isolated hepatocytes. Anesth Analg 1990;70:22–8.

This study has examined whether adverse halothane effects on liver-cell energy metabolism are influenced by the availability of alternate substrates for energy-generating reactions. Halogenated volatile anesthetics affect both energy supply and energy demand in tissues, and cellular energy deficits have been implicated in anesthetic hepatotoxicity. Using hepatocytes isolated from fed rats either pretreated with phenobarbital or not treated (+PB or −PB cells, respectively), we studied the cellular energetic effects of providing fatty acid (oleic acid) along with glucose as substrate(s) for energy metabolism, while exposing the cells to 0%–2% halothane. In −PB cells incubated with glucose alone, there were halothane dose-related decreases in the oxygen (O_2) consumption rate (Vo_2) and in the balance between adenosine triphosphate (ATP) supply and demand (ATP/ADP ratio), but no effect on lactate metabolism (lactate consumption or production) over the 10-min incubation period. Adding oleate along with glucose (a) raised Vo_2 but lowered ATP/ADP in the absence of halothane; (b) eliminated the decreases in Vo_2 and ATP/ADP seen when halothane was introduced; and (c) increased lactate consumption in both the presence and absence of halothane. In +PB cells, Vo_2 was higher, ATP/ADP lower, and lactate consumption also lower than in −PB cells under comparable conditions. Halothane or oleate effects, or both, on energy metabolism were thus qualitatively similar in +PB and −PB cells, except that in +PB cells incubated without oleate, lactate formation developed as halothane was increased from 0% to 2%, reflecting activation of glycolysis due to insufficient mitochondrial ATP production. Our work with isolated hepatocytes thus suggests that glucose-supported aerobic energy metabolism was only modestly inhibited by halothane at 0% to 2%, in contrast to previous results using isolated perfused liver and a single, higher halothane concentration. We also found that oleate had mixed effects on hepatocellular energy status when provided along with glucose: halothane's inhibitory effect on ATP supply was reversed, as reported by others; but oleate also increased ATP demand through other, unidentified action(s) not involving halothane. Fatty acids are always available to liver cells in vivo, although at somewhat lower concentrations in fed animals than were used in these in vitro incubations. The general conclusion supported by this study is that by means of any direct *action on liver cells, halothane does* not *interfere with energy metabolism at typical in vivo levels of substrates, O_2, and halothane. +PB cells function at higher rates of energy demand and at lower ATP/ADP than do −PB cells and are thus more susceptible to development of energy deficits.*

Key Words: ANESTHETICS, VOLATILE—halothane. LIVER, METABOLISM, HEPATOTOXICITY. METABOLISM, HEPATIC, HALOTHANE EFFECTS.

This study was undertaken to determine the relationship between adverse halothane effects on hepatocellular energy balance and the availability of alternate metabolic fuels to support energy-generating reactions. Because halothane administration has been associated with hepatocellular necrosis (see References 1–3 for reviews), the effects of this agent on various metabolic reactions essential to hepatocellular viability have been actively studied. Anesthetic-associated decreases in systemic and regional oxygen (O_2) consumption (4,5) raised the possibility that general anesthetics as a group might precipitate hepatic injury by inhibiting mitochondrial oxidative phosphorylation. The latter process meets most of the cell's energy needs by using O_2 to complete the degradation of metabolic fuels and using the energy released therefrom to drive the formation of adenosine triphosphate (ATP) from adenosine diphosphate (ADP) (Figure 1; see Reference 6 for review).

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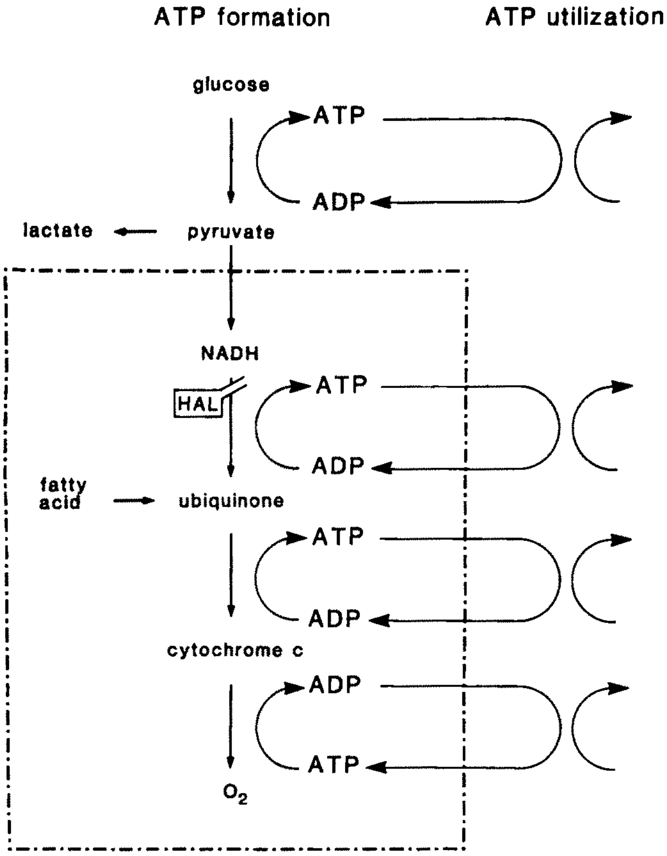

Figure 1. Schematic diagram of sequence and localization of various reactions important to energy metabolism within a liver cell. The *rectangle* represents the mitochondrial membrane. Other intracellular organelles are not shown.

In isolated mitochondria, halothane even at sub-MAC doses inhibited oxidative phosphorylation at the step of nicotinamide adenine dinucleotide (reduced form) (NADH) oxidation (Figure 1; [7]). Although pyruvate, the major metabolite of glucose, and most other energy-rich substrates in liver cells are indeed oxidized by way of NADH, a relative few, such as fatty acids, donate their electrons directly to ubiquinone. These alternate substrates thus bypass the NADH oxidation step and reverse the inhibition of oxidative phosphorylation by anesthetics (Figure 1; see Reference 8 for review).

Finally, Figure 1 also illustrates that cellular energy status represents a dynamic balance between ATP production—mainly via mitochondrial oxidative phosphorylation—and ATP utilization by other reactions located mainly outside mitochondria. As any or all reactions involving ATP could in principle be affected by an anesthetic, overall anesthetic effects on cellular energy status can be meaningfully determined only in a tissue preparation containing intact cells, assuring that ATP-producing and ATP-utilizing reactions are present in physiological proportions. In the case of liver, this important point was first addressed by Biebuyck et al. (9), who measured halothane effects on energy metabolism in isolated perfused rat liver. Finding hepatic ATP/ADP decreased by halothane exposure, these workers inferred that halothane inhibited ATP production to a greater extent than ATP utilization, and they predicted that hepatic energy deficits developed in vivo as a result of halothane exposure. They also showed that addition of fatty acid (oleic acid) to the liver perfusate greatly reduced the deleterious effect of halothane on hepatic energy metabolism in vitro (10).

However, these landmark studies of Biebuyck and colleagues used halothane at only a single concentration of 2.5%, a value at least twice the ED_{50} and above the range of steady state concentrations attained in humans or animals under clinically relevant conditions. In recent work with intact isolated hepatocytes under steady states of energy metabolism simulating those in intact liver, we too found significant energy deficits (i.e., decreases in ATP/ADP) at 2% and 3% halothane but not at 1% halothane (11), a value closer to the typical maintenance dose. Another problem with any biochemical study carried out on intact liver is that even small samples lump together tissue from anatomically and biochemically diverse microenvironments (12). The importance of this sublobular heterogeneity—hence the need to eliminate it as a variable when correlating anesthetic exposure with specific cellular biochemical responses—is indicated by the fact that halothane or hypoxia-induced hepatocellular necrosis in animal models, or both, is characteristically confined to pericentral (perivenous) zones of liver lobules, while periportal regions are spared (13,14). Our work has therefore used isolated intact hepatocytes, which contain the full complement of metabolic activities found in intact tissue yet can be studied under uniform and precisely known pericellular environments.

For the reasons cited above, we have in the present study used isolated hepatocytes to characterize more precisely the hepatocellular energetic effects of including fatty acid (oleic acid) along with glucose as substrate(s) during exposure of the cells to clinically relevant steady state concentrations of halothane (0%, 1%, and 2%) and O_2. As hepatocytes isolated from rats pretreated with phenobarbital were more susceptible to energy deficits than those from untreated animals (11,15,16), phenobarbital pretreatment has also been included in this study as an independent variable.

Methods

Adult male F344 rats having free access to drinking water and standard laboratory diet were used according to the following protocol, which was approved by the animal research committee of our institution. Phenobarbital (PB)-treated rats were given 0.1% PB in the drinking water for 5–7 days before being killed. Isolated hepatocytes were prepared after in situ perfusion of the liver with Krebs' bicarbonate buffer containing collagenase, exactly as previously described (15). Experiments were carried out by incubating the isolated cells after their resuspension in fresh Krebs' buffer without collagenase. Glucose (5 mM) was present in all incubations. Oleic acid, when present, was added as the sodium salt (sodium oleate) to a final concentration of 1 mM, along with 2% bovine serum albumin: one part stock solution of sodium oleate (10 mM) in 20% albumin was stirred into nine parts Krebs' buffer stock solution. (For incubations that did not contain oleate, the same dilution was obtained by adding one part water to nine parts Krebs' stock.) In addition to glucose ± oleate, the complete Krebs' buffer-based incubation medium contained the following components and final concentrations: 142 mM sodium, 5 mM potassium, 1 mM magnesium, 1 mM calcium, 2 mM phosphate, 24 mM bicarbonate, and 120 mM chloride. The medium was kept equilibrated with a gas phase containing 5% carbon dioxide (CO_2) to maintain pH at 7.4.

As before, cell suspensions were incubated at 37°C in a 1.8-mL glass chamber containing a built-in polarographic O_2 electrode for continuous recording of extracellular Po_2 (11,16). Vigorous magnetic stirring eliminated heterogeneity in the concentrations of cells, substrates, and O_2 within the incubation mixture. When the chamber was completely filled with cell suspension (4×10^6 cells/mL) and stoppered (= closed system), thereby eliminating O_2 supply, O_2 demand (Vo_2) was measured directly as a linear decrease of Po_2 with time (11,16). This slope was measured before and after each of two successive additions of 9 μL of 1% halothane solution in ethanol; the resulting final concentrations of 10 and 20 mg/100 mL dissolved halothane were equal to those that would have been attained by equilibration of aqueous medium with halothane vapor concentrations of 1% and 2%, respectively. Changes in Vo_2 resulting from injection of ethanol-diluted anesthetic were corrected for the slight decrease in Vo_2 (about 2% per addition) observed in control incubations with ethanol alone.

For measuring metabolites as indicators of cellular energy status under conditions of balanced O_2 supply and demand simulating those in vivo, 1.2 mL of cell suspension (containing 1.2×10^7 hepatocytes) was added to the chamber, which was left unstoppered (= open system). With an anesthesia machine used as gas mixer and flowmeter, fresh gas mixture was circulated continuously across the surface of the cell suspension (11,15). The percentage of O_2 in the gas mixture was adjusted to produce in the cell suspension a constant Po_2 = 30 mm Hg (in the low-normal range for hepatic central venous blood). In addition to O_2, the gas mixture also contained halothane, 5% CO_2, and N_2 for a total of 100%. Exactly 10 min after these steady states of O_2 and energy metabolism (constant Po_2) were achieved, the suspensions were quenched with perchloric acid. Precipitated protein was removed by centrifugation, the clear extract was neutralized with potassium hydroxide, and ATP, ADP, and lactate were determined by the same chromatographic and enzymatic techniques used previously (15). The ratio of ATP to ADP was used as the principal indicator of cellular energy status, as it reflects the relative rates of ATP-supplying and ATP-consuming intracellular reactions. Lactate metabolism was expressed as Δ lactate, the difference between lactate concentrations at the beginning and end of the 10-min steady-state period of incubation. Negative numbers represented net lactate utilization by the cells, positive numbers net lactate production.

The combined dependence on halothane concentration, presence or absence of added oleate, and presence or absence of prior PB treatment was assessed separately for each of the three energetic variables using three-way analysis of variance with repeated measures on halothane and oleate, as all three concentrations of halothane in both the absence and presence of added oleate were examined with every hepatocyte preparation. When analysis of variance showed significant dependence on halothane concentration, values at 1% or 2% halothane were compared with those at 0% halothane within each of the four groups (±oleate, ±PB) by paired *t*-test. The latter was also used to assess the effect of including oleate at individual halothane concentrations in either +PB or −PB cells. As the presence and absence of prior PB treatment are represented by two different groups of hepatocyte preparations, the *t*-test for independent (unpaired) samples ascertained the effect of PB treatment for +oleate or −oleate groups at individual halothane concentrations. $P < 0.05$ was considered statistically significant.

Table 1. Rates of Oxygen Consumption (Vo_2) in Isolated Hepatocytes Exposed to Halothane

Halothane concentration (%)	Vo_2 (nmol·10^7 cells^{-1}·min^{-1})			
	−PB cells		+PB cells	
	Glucose alone	Glucose + oleate	Glucose alone	Glucose + oleate
0	31 ± 8	34 ± 9	42 ± 8	42 ± 6
1	30 ± 8	34 ± 9	47 ± 7	46 ± 6
2	25 ± 7[d]	31 ± 7[e]	45 ± 7	43 ± 6
	a	*b*	*c*	*c*

PB, phenobarbital. Values given are mean ± SEM for six different cell preparations.

[a] Halothane-related difference within group by analysis of variance (ANOVA).

[b] Different from corresponding "glucose alone" group by ANOVA.

[c] Different from corresponding "−PB cells" group by ANOVA.

[d] Different from 0% and 1% halothane value by *t*-test.

[e] Different from corresponding "glucose alone" value by *t*-test.

Table 2. Adenosine Triphosphate Supply and Demand Balance (ATP/ADP) in Isolated Hepatocytes Exposed to Halothane

Halothane concentration (%)	ATP/ADP			
	−PB cells		+PB cells	
	Glucose alone	Glucose + oleate	Glucose alone	Glucose + oleate
0	3.60 ± 0.26[d]	2.76 ± 0.18[e]	2.74 ± 0.35	2.13 ± 0.26
1	2.65 ± 0.23	2.55 ± 0.30	1.73 ± 0.13	1.91 ± 0.10
2	2.43 ± 0.17	2.44 ± 0.29	1.74 ± 0.16	2.29 ± 0.25
	a	*b*	*a,c*	*c*

PB, phenobarbital. Values given are mean ± SEM for six different cell preparations.

[a] Halothane-related difference within group by analysis of variance (ANOVA).

[b] Different from corresponding "glucose alone" group by ANOVA.

[c] Different from corresponding "−PB cells" group by ANOVA.

[d] Different from 1% and 2% halothane values by *t*-test.

[e] Different from corresponding "glucose alone" value by *t*-test.

Table 3. Lactate Metabolism (Δ Lactate) in Isolated Hepatocytes Exposed to Halothane

Halothane concentration (%)	Δ Lactate (nmol/10^7 cells)			
	−PB cells		+PB cells	
	Glucose alone	Glucose + oleate	Glucose alone	Glucose + oleate
0	−77 ± 39	−217 ± 81	−99 ± 51	−75 ± 38
1	−124 ± 47	−219 ± 72	−55 ± 18	−51 ± 44
2	−10 ± 51	−172 ± 58	+56 ± 53[d]	−75 ± 13[e]
		b	*a*	*c*

PB, phenobarbital. Values given are mean + SEM; $n = 6$.

[a] Halothane-related difference within group by analysis of variance (ANOVA).

[b] Different from corresponding "glucose alone" group by ANOVA.

[c] Different from corresponding "−PB cells" group by ANOVA.

[d] Different from 0% halothane value by *t*-test.

[e] Different from corresponding "glucose alone" value by *t*-test.

Results

Tables 1–3 show the values of O_2 consumption rate (Vo_2), balance between ATP supply and demand (ATP/ADP) and changes in lactate level (Δ lactate), respectively, obtained from incubations of isolated hepatocytes under differing conditions of halothane exposure, substrate availability, and PB pretreatment. For −PB cells incubated with glucose alone, a progressive increase in halothane concentration from 0% to 2% significantly decreased both Vo_2 and ATP/ADP, without a consistent effect on Δ lactate (column 1, Tables 1–3). Inclusion of oleate eliminated the halothane-associated decrease in ATP/ADP by lowering the ATP/ADP value seen at 0% halothane (column 2 vs 1, Table 2). Added oleate also raised Vo_2 and increased lactate utilization—i.e., made Δ lactate more negative—compared with the glucose-alone values at corresponding halothane concentrations (column 2 vs 1, Tables 1 and 3).

The +PB cells resembled the −PB cells in that 1% and 2% halothane decreased ATP/ADP when glucose alone was the substrate (column 3, Table 2); similarly, the inclusion of oleate eliminated this halothane-related decrease in ATP/ADP by lowering the ATP/ADP value at 0% halothane rather than by raising the ATP/ADP values at 1% and 2% (column 4 vs 3, Table 2). However, unlike −PB cells, +PB cells showed a shift toward lactate formation with increasing halothane in the presence of glucose alone—most evident in the positive value of Δ lactate, signifying net lactate production, which appeared at 2% halothane (column 3, Table 3). Furthermore, Vo_2 increased at 1% halothane before decreasing at 2% (column 3, Table 1). Supplementation with oleate eliminated lactate formation at 2% halothane in +PB cells (column 4 vs 3, Table 3); whereas halothane's effect on Vo_2 was not significantly altered by including oleate (column 4 vs 3, Table 1).

In comparing absolute values of corresponding measurements in −PB and +PB cells, the latter showed generally higher Vo_2, lower ATP/ADP, and less negative Δ lactate values than did −PB cells under comparable incubation conditions (column 3 vs 1 and 4 vs 2, Tables 1–3).

Discussion

The results presented above indicate that under homogeneous and well-defined conditions, three factors relevant to halothane exposure—anesthetic concentration, nature of energy source, and rate of anesthetic metabolism—acted directly on liver cells to produce statistically significant effects on cellular energy status. These effects were evaluated by three complementary measures of energy metabolism: overall rate of O_2-dependent metabolism (Vo_2), balance between ATP supply and demand (ATP/ADP), and disposal or formation of lactate (Δ lactate).

Halothane Concentration Effects

In −PB cells incubated with glucose alone, the decreases in Vo_2 and ATP/ADP produced by halothane are consistent with the latter's known ability to limit mitochondrial energy generation by inhibiting NADH oxidation in the respiratory chain (7). The lack of a dose-related halothane effect on Δ lactate suggests that at typical in vivo anesthetic concentrations, halothane's inhibitory effects on hepatocellular energy metabolism may be of marginal physiologic significance because lactate metabolism, an important hepatic function (see below), was not significantly altered by introducing halothane to −PB cells. These results are in general agreement with those of Biebuyck et al. (9), who used isolated perfused liver, with the exception of findings on lactate metabolism: these workers reported substantial net production of lactate by halothane-exposed isolated perfused liver from fed rats, persisting even when oleate was provided. In contrast, at a halothane concentration only 0.5% lower (2%), we saw no lactate formation in −PB cells even in the absence of oleate. This considerable discrepancy in results with such a small difference in halothane concentration suggests that one or more other variables may have been contributing to the differences. One possibility is that in the intact liver, besides inhibiting the mitochondrial respiratory chain, halothane might also have changed intrahepatic perfusion patterns so that focal hypoxia developed. Lactate formation due to hypoxia would *not* have been reversible by oleate, and isolated cells are not dependent on perfusion.

Oleate Effects

The ability of added fatty acid to eliminate halothane-related decreases in Vo_2 and ATP/ADP and to enhance lactate disposal—i.e., make Δ lactate more negative—in −PB cells is consistent with oleate's demonstrated ability to reverse halothane's inhibition of hepatic O_2 consumption and coupled ATP production (10). However, the pattern of our results indicates that oleate's effects on hepatocellular energy status were not limited to simply increasing energy supply by counteracting halothane's inhibitory effects on mitochondria. Had oleate acted only in that way, it should not have increased Vo_2 and decreased ATP/ADP in the absence of anesthetic (0% halothane) compared with glucose alone.

These additional effects of oleate on hepatocellular energy metabolism can be explained by the possibility that oleate also increases hepatocellular energy *demand*. Our data further suggest that oleate increased energy demand in liver cells by activating glucose formation (gluconeogenesis) from lactate that was present in the cell suspension. Gluconeogenesis, important for the recycling of lactate generated in other tissues (or in the liver itself) as an end product of glucose metabolism, utilizes ATP and is inhibited when hepatocellular energy status is compromised (17). Furthermore, gluconeogenesis is promoted by specific intracellular regulatory mechanisms in the liver when fatty acid is available as an alternate substrate for the support of mitochondrial ATP production. Increases in acetyl-coenzyme A (and NADH) generated by fatty acid oxidation enhance gluconeogenesis from either lactate or pyruvate (which are readily interconvertible via lactate dehydrogenase) through two complementary mechanisms: (a) pyruvate dehydrogenase is inhibited, preventing pyruvate's (lactate's) entry into the tricarboxylic acid cycle and its eventual complete oxidation; and (b) pyruvate carboxylase is activated, favoring pyruvate's (lactate's) conversion to oxaloacetate and thence to glucose (18). Biebuyck et al. (10) reported increased Vo_2 when rat livers isolated from fed animals (and thus containing ample endogenous glucose in the form of glycogen) were perfused with oleate; however ATP, ADP, and lactate were not measured on those preparations to permit detailed comparison of our results with theirs.

Phenobarbital Effects

The +PB cells showed both qualitative and quantitative differences from −PB cells in the responses of energy metabolism to halothane or oleate, or both. Higher Vo_2 values in the absence of halothane in +PB compared with −PB cells are consistent with elevated baseline O_2 consumption reported in livers of PB-treated animals (19). The biphasic response of Vo_2 to increasing halothane concentration—higher values at 1% than at either 0% or 2% halothane—duplicates the finding of our previous study and reflects the superimposed contribution of an extra O_2-consuming process, the P450-mediated (oxidative) degradation of halothane, which is much more rapid in hepatocytes isolated from PB-treated rats (11). In the present study, this P450-mediated increase in Vo_2 in +PB cells may have masked halothane-related decreases in Vo_2 with glucose alone and also the increases in Vo_2 with glucose + oleate similar to those seen in −PB cells. An alternative possibility—that halothane- and/or oleate-related effects on energy metabolism analogous to those seen in −PB cells were simply absent in +PB cells—is ruled out by the results of the ATP/ADP and Δ lactate measurements. The pattern of ATP/ADP dependence on anesthetic or substrate, or both, in +PB cells was virtually identical to that in −PB cells, although absolute values of ATP/ADP were significantly lower as a group in +PB cells than in −PB cells. On the other hand, halothane- and oleate-related effects on lactate metabolism in +PB cells differed qualitatively as well from those in −PB cells. In +PB cells incubated with glucose alone, lactate metabolism steadily shifted from net utilization (−Δ lactate) toward net production (+Δ lactate) as halothane increased from 0% to 2%. This halothane-related trend toward activation of glycolysis, reflecting insufficient mitochondrial ATP production in +PB cells, was absent when oleate was included, although the extent of lactate disposal (magnitude of −Δ lactate) remained significantly less in +PB cells than in −PB cells at corresponding halothane concentrations.

Interactions and Significance of Halothane, Oleate, and Phenobarbital Effects in Isolated Hepatocytes

Isolated hepatocytes responded to the presence of halothane or oleate, or both, with changes in energy metabolism generally consistent with those observed in another intact cell preparation, isolated perfused liver (9,10). In both systems energy deficits arising from halothane-inhibited NADH oxidation were alleviated by the ability of oleate to bypass that step in donating electrons to the mitochondrial respiratory chain. Differences between the results obtained in the two systems may be ascribed mainly to the fact that the isolated hepatocytes were studied at lower anesthetic concentrations—and perhaps also that a broader range of cellular environments was represented in samples of intact liver.

An additional action of oleate newly reported in the present study is an increase in energy demand in liver cells of fed animals. Increased lactate utilization was occurring concurrently, and conversion of lactate to glucose (gluconeogenesis) is known to consume ATP. On the other hand, gluconeogenesis is not an active process in the livers of fed animals, and there are other reactions that could consume lactate. Additional experiments correlating changes in glucose, oleate, and lactate concentrations would be needed to provide a more complete accounting of substrate utilization in this situation. Whatever the specific reaction(s) responsible, increased ATP demand in the presence of oleate would tend to counteract the benefit of increased ATP supply arising from oleate's reversal of mitochondrial inhibition due to halothane.

The generally higher Vo_2, lower ATP/ADP, and reduced lactate disposal (smaller values of −Δ lactate) in +PB cells compared with −PB cells support previous suggestions that +PB cells operate at a relative energy deficit (2,15). These differences between +PB and −PB cells are seen in the absence as well as the presence of halothane, indicating that enhanced halothane metabolism is not the sole contributor to energy deficits of internal origin produced in liver cells by prior PB treatment. The relative importance of these intrinsic changes in liver cells and the various extrinsic factors such as hypoxia, reduced blood flow, and anesthetic exposure that adversely affect hepatocellular energy supply and that are also present in various animal models of anesthetic-induced hepatotoxicity remains to be established (1).

This study has further elucidated rapidly developing shifts in energy metabolism occurring within isolated liver cells under simulated physiologic conditions of volatile anesthetic exposure (11,15) and has examined the influence of energy substrate availability on those changes. The contribution of substrate availability to promoting or preventing anesthetic-mediated hepatotoxicity occurring over longer exposure periods and in the presence of other variables operating in vivo remains to be determined by further experiments using models and conditions that specifically address these questions. In this regard, Biebuyck and Lund (20) found considerably less impairment of energy metabolism by halothane in the liver of the intact rat than in the isolated perfused organ. They attributed these differences to the ability of an intact circulation and hormone-mediated metabolic interactions of liver with other tissues to counteract factors such as substrate lack and product accumulation that could develop in an isolated in vitro system. It should also be noted that the halothane concentration employed was substantially lower in vivo (1.5%) than it was in vitro (2.5%). The present and previous studies suggest that anesthetic effects on hepatocellular energy balance may depend strongly on anesthetic concentration within this range (11).

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Postoperative Pain After Inguinal Herniorrhaphy with Different Types of Anesthesia

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In a randomized, double-blind study, postoperative pain was assessed in 36 patients undergoing inguinal herniorrhaphy with three types of anesthesia: general (thiopental-nitrous oxide-halothane); general with the addition of local (infiltration of the abdominal wall with 0.25% bupivacaine along the line of the proposed incision); and spinal (0.5% bupivacaine). The severity of constant incisional pain, movement-associated incisional pain, and pain upon pressure applied to the surgical wound using an algometer was assessed with a visual analogue self-rating method at 24 h, 48 h, and 10 days after surgery. The addition of local anesthesia significantly decreased the intensity of all types of postoperative pain. This effect was especially evident with constant incisional pain that disappeared almost completely 24 h after surgery. With pain caused by pressure on the site of the surgical incision, the pain score difference between general and general plus local anesthesia was obvious even 10 days after the surgery (with 0.4-kg/cm^2 pressure, the pain scores were 16 ± 3 vs 2 ± 1, $P < 0.01$). The difference in postoperative pain scores between spinal and general anesthesia groups indicated that spinal anesthesia also decreases the pain intensity. However, this decrease is less pronounced than that seen with the addition of local anesthesia: movement-associated pain scores 24 h after surgery were 72 ± 5 in the general anesthesia group, 40 ± 6 in the spinal anesthesia group, and 16 ± 3 in the general plus local anesthesia group (with $P < 0.002$ between the groups).

Our results indicate that postoperative pain after inguinal herniorrhaphy can be significantly decreased if the surgery is performed with the use of local or spinal anesthesia. We hypothesize that neural blockade, by preventing nociceptive impulses from entering the central nervous system during and immediately after surgery, suppresses the formation of the sustained hyperexcitable state in the central nervous system that is responsible for the maintenance of postoperative pain.

Key Words: PAIN, POSTOPERATIVE.

There is a renewed interest in the use of local anesthesia for reduction of postoperative pain (1–3). It was reported that infiltration of the abdominal wall along the line of the proposed incision for inguinal herniorrhaphy with 0.25% bupivacaine results in a postoperative pain-free period of approximately 10 h (4). Administration of a local anesthetic in the wound before its closure (bupivacaine instillation or application of lidocaine aerosol) has been found to decrease opioid requirements and accumulated pain score during the first 24 h postoperatively (2,3). In the initial studies, to obtain long-lasting postoperative analgesia, the investigators implanted catheters in the surgical wound and injected local anesthetics at regular intervals after surgery (5–7).

The aims of the present study were to determine (a) whether local anesthesia used during surgery decreases the severity of pain beyond the immediate postoperative period, when the pain relief cannot be explained by prolonged presence of the local anesthetics in the body; and (b) whether spinal anesthesia (which does not provide the significant direct effect of a local anesthetic on tissues in the area of surgery) relieves postoperative pain similar to local anesthesia.

Methods

With approval from the Institutional Human Investigation Committee and informed consent, 36 male patients, 35–75 yr of age, scheduled for elective

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inguinal hernia repair at the Safed Hospital, were investigated in a double-blind, randomized study. Patients with severe hepatic, renal, or cardiovascular disease were excluded. Hernia repair was carried out by the same surgeon using the Bassini technique. The patients were divided randomly (systematic random sample technique) into three groups: general anesthesia (G), general plus local anesthesia (G + L), and spinal anesthesia (S), with 12 patients in each group. In the G group, patients received preanesthetic medication consisting of atropine (0.5 mg SC) and promethazine (25 mg IM). Anesthesia was induced with thiopental (4 mg/kg), and after the administration of 1 mg of pancuronium to prevent fasciculations, tracheal intubation was performed with the aid of succinylcholine (1 mg/kg). After intubation, 5 mg of pancuronium was given, with additional doses (1 mg) as indicated during surgery. Anesthesia was maintained with nitrous oxide in oxygen (N_2O/O_2; 2:1) and 0.5% halothane. At the conclusion of the surgery, 1 mg of atropine followed by 2.5 mg of neostigmine was administered. No narcotic was used for premedication or during surgery. In the G + L group, in addition to the general anesthesia performed as described above, subcutaneous and intramuscular infiltration of the abdominal wall with 0.25% bupivacaine (40 mL) along the line of the proposed incision was made 5 min before the surgery. About 2 mL of the bupivacaine solution was injected around the neck of the sac at the appropriate stage of the surgery. In the S group, under conscious sedation with midazolam (0.07 mg/kg IV), the spinal anesthesia was achieved using 0.5% solution of bupivacaine (12.5 mg). The subarachnoid puncture was performed at the L3-4 interspace with a 25-gauge needle.

Postoperatively, patients from all three groups were treated for pain in exactly the same way. When a patient complained of pain, meperidine (50 mg IM), was given, and the time from the end of the surgery to the first request for analgesic was recorded (time to first analgesic). After the first injection each patient received 25 mg of meperidine every 4 h on the first day and every 6 h on the second day after surgery. Starting with the third day the patients were given 500 mg of acetaminophen every 4 h orally.

The intensity of postoperative pain was assessed by the patients blinded to the possible association between the type of anesthesia and postoperative pain. The investigator participating in the pain assessment was blinded to the patient group. The assessment was made three times in each patient: at 24 h, 48 h, and 10 days after the surgery (at follow-up visit). The assessment of pain was performed with a visual analogue self-rating method (8). The visual analogue scale consisted of a 100-mm horizontal line without gradation connecting points marked as "no pain at all" and "as severe as it could be." All assessments of pain intensity were made 3–4 h after meperidine administration. The patients were told to indicate how they felt at the moment by placing a mark perpendicular to the line. The scales were scored by measuring the distance (in millimeters) of the perpendicular mark from the left side of the line.

Table 1. Characteristics of Patients

	Types of anesthesia		
Variable	General	General plus local	Spinal
n (all males)	12	12	12
Age (yr)	59 ± 9	53 ± 7	54 ± 13
Weight (kg)	69 ± 9	73 ± 10	71 ± 14
Duration of surgery (min)	32 ± 6	31 ± 5	30 ± 6

Values are mean ± SD.

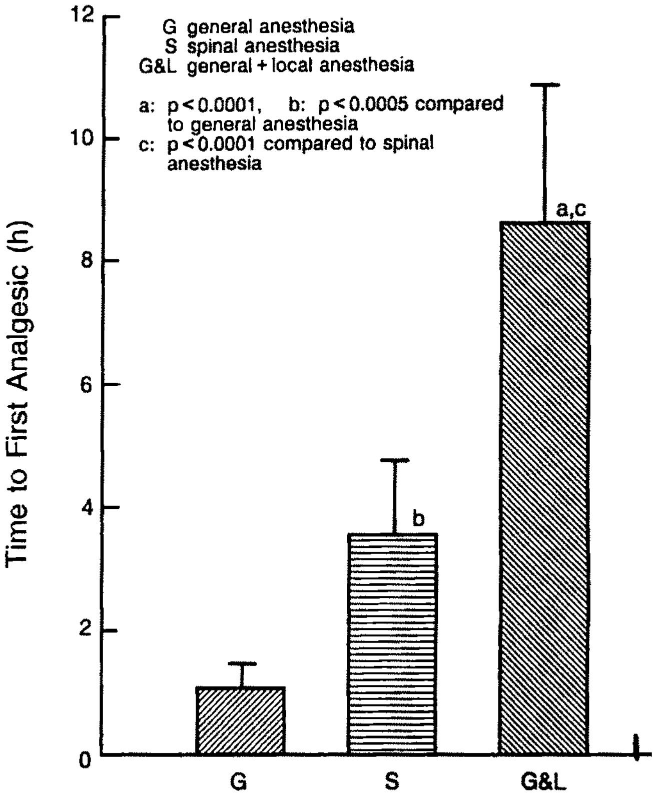

Figure 1. Times from the end of the surgery to the first request for analgesic after three different types of anesthesia (mean ± SEM).

Three types of pain were assessed: constant incisional pain, movement-associated incisional pain, and pain upon pressure on the surgical wound. The movement-associated incisional pain was assessed,

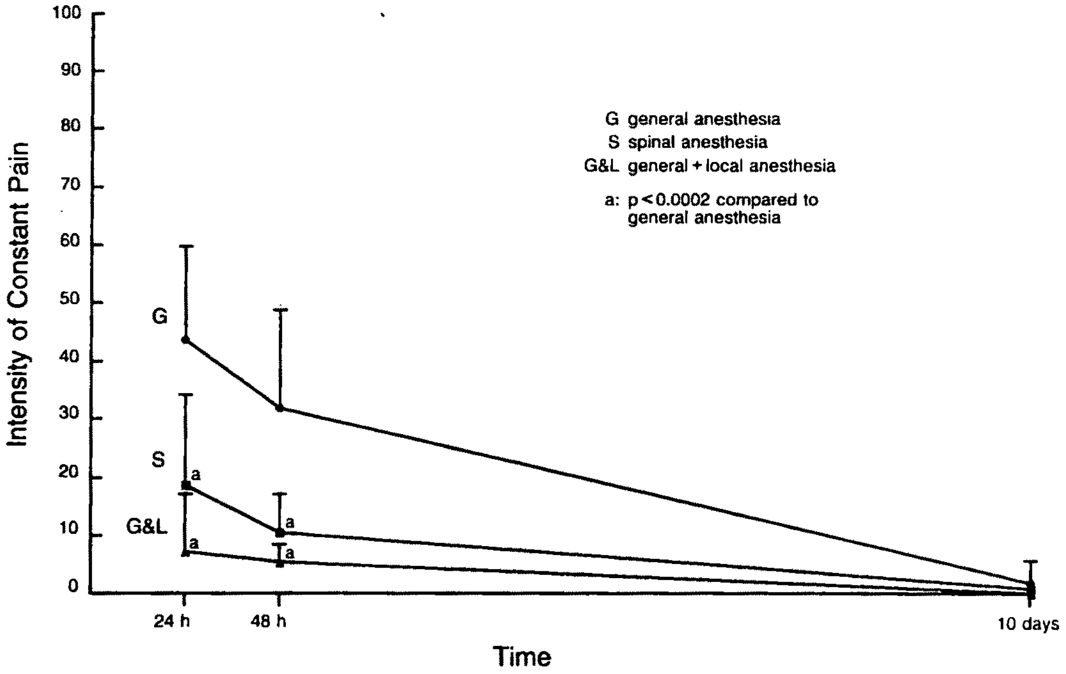

Figure 2. Intensity of constant postoperative incisional pain after three different types of anesthesia. The pain score is presented in millimeters on a 100-mm visual analogue scale (mean ± SEM).

on request of an investigator, after the patient got out of the bed. An algometer (PDT Co., Great Neck, N.Y.) with a pressure surface of 4 cm^2 was used for the determination of the pain on pressure. The pressure was applied on the wound for 10 s through the dressing. At 24 h and 48 h 0.2-kg/cm^2 and 0.3-kg/cm^2 pressures were used, and on day 10, 0.4 kg/cm^2 and 0.6 kg/cm^2. Severity of the pain resulting from pressure on the wound was also assessed with the visual analogue self-rating method. In addition, the threshold for wound pain elicited by pressure was measured. With the use of the algometer, pressure on the wound was increased at a constant speed of 0.02 kg·cm^{-2}·s until the patient indicated the pressure was painful. The pain threshold was measured 24 h, 48 h, and 10 days after surgery.

The data were summarized as mean ± SEM for each group. A one-way analysis of the variance was used to assess the differences in mean pain scores and in mean times to first administration of meperidine among the three groups utilized (9). Multiple comparisons among pairs of stage means used the Fisher's protected least significant difference test (9,10). Differences were declared statistically significant if $P < 0.05$.

Results

The study groups were comparable with respect to age, weight, and duration of surgery (Table 1). In addition, all patients were male and had the same type of surgery performed by the same surgeon. The duration of analgesia (time from the end of the surgery to the first request for analgesic) was 64 ± 8 min in group G, 212 ± 21 min in group S, and 515 ± 39 min in group G + L, with statistically significant differences between each of the groups (Figure 1). The most dramatic effect of local and spinal anesthesia was observed with regard to the constant incisional pain. In group G + L, this type of pain was essentially absent 24 h after the surgery at a time when the pain intensity score in group G was 44 ± 5 and 32 ± 5 at 24 h and 48 h respectively. In group S the constant pain score was significantly lower than in group G and not statistically different from group G + L (Figure 2). The score of the movement-associated incisional pain at 24 h was the highest in group G (72 ± 5) and the lowest in group G + L (16 ± 3), with group S occupying the intermediate position (40 ± 6). At 48 h the movement-associated pain scores were proportionally decreased in the G and S groups without any significant change in group G + L (Figure 3).

Pain intensity at pressure on the wound also was highest in group G and lowest in group G + L, with group S in the intermediate position, for both 24 h and 48 h. Ten days after surgery the difference between the G and the G + L groups still was present

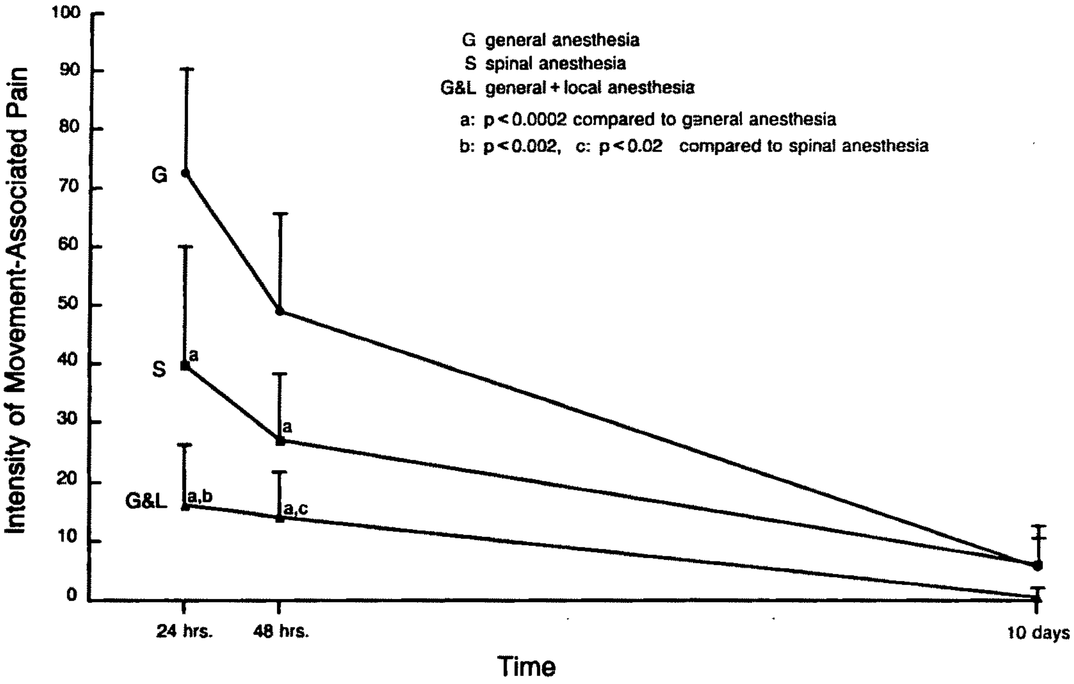

Figure 3. Intensity of movement-associated postoperative incisional pain after three different types of anesthesia. The pain caused by getting out of bed is presented in millimeters on a 100-mm visual analogue scale (mean ± SEM).

(pain score 16 ± 3 vs 2 ± 1, $P < 0.01$, with 0.4-kg/cm^2 pressure, and 35 ± 4 vs 16 ± 3, $P < 0.01$, with 0.6-kg/cm^2 pressure). At the same time, no difference was found between the G and S groups (Figure 4). The threshold to pain on pressure data basically confirmed the pain intensity to pressure results. The wound pain threshold was much lower in the G and S groups than in the G + L group. The difference between the G and S groups was statistically significant only at 48 h (Figure 5).

Discussion

The addition of local anesthesia to general anesthesia resulted in an increase in the postoperative time to the first request for analgesic from 1 h to approximately 9 h, at a time when this period with spinal anesthesia was 3.5 h. A prolonged pain-free period (10 h) after local anesthesia (0.25% bupivacaine administered before incision) for inguinal herniorrhaphy was reported by Kingsnorth et al. (4). It is well known that analgesia with bupivacaine-induced infiltration anesthesia lasts longer than with bupivacaine spinal anesthesia and that some bupivacaine-induced peripheral nerve blocks have anesthetic effect up to 12 h (11). It should be noted also that analgesia after bupivacaine infiltration persists longer than does anesthesia (12). If given this, the prolonged period from the end of surgery to the first request for analgesic in our G + L anesthesia group is not surprising.

Our results indicate that the addition of local anesthesia to general anesthesia significantly decreases the intensity of postoperative pain. This effect was especially evident with constant incisional pain, which was almost completely absent at both 24 and 48 h after surgery. With the pain caused by pressure on the site of the surgical incision, the pain score difference between general anesthesia alone and general anesthesia plus local anesthesia was obvious even 10 days after the surgery.

Two recent studies on the use of local anesthetics in the surgical wound before closure of the incision also demonstrate a significant reduction in postoperative pain at 24 h but not at 48 h after surgery (2,3). The discrepancy between these results and our present findings might be due to the fact that in our study the postoperative use of analgesics was the same in all three groups of patients. Therefore, the postoperative pain difference between the groups could find its expression only in one index—pain score (otherwise this difference might be disguised by fragmentation of the changes between two indices: consumption of analgesics and pain score). Patel et al. (13), using a single injection of bupivacaine into the wound after cholecystectomy, demonstrated a

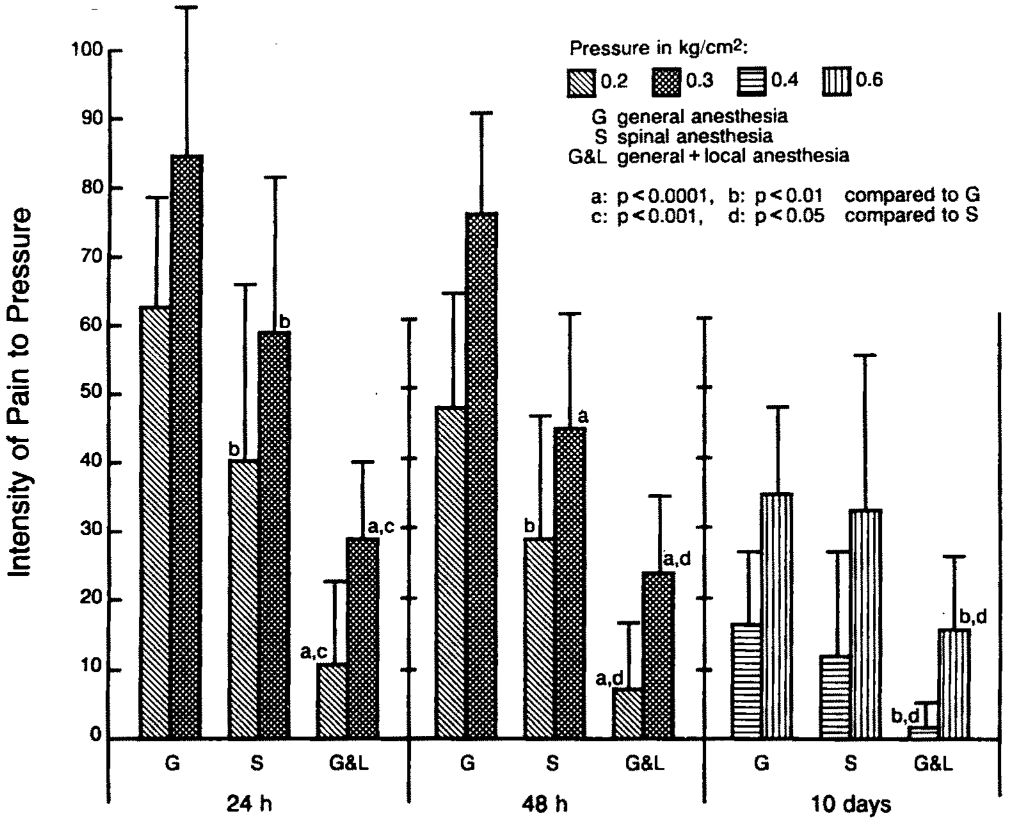

Figure 4. Intensity of pain caused by pressure on the surgical wound after three different types of anesthesia. The pain score is presented in millimeters on a 100-mm visual analogue scale (mean ± SEM).

reduction in postoperative narcotic requirement for 3 days and a decrease in deterioration of pulmonary function tests after surgery. A subsequent study with continuous infusion of bupivacaine into an upper abdominal wound after cholecystectomy did not report better postoperative pain relief than perfusion with normal saline (14).

The difference in postoperative pain intensity between the spinal anesthesia group and the group given general anesthesia alone seen in our study indicates that spinal anesthesia also decreases postoperative pain. However, this decrease was less pronounced than that with local anesthetic injected into the operative site, especially with movement-associated pain and pain caused by the pressure on the wound. Pain upon pressure on the site of the surgical wound 10 days after surgery performed under spinal anesthesia was not different from that seen in the group given general anesthesia alone. We suggest that a less profound effect of spinal anesthesia on postoperative pain was due to a shorter duration of its effect (3.5 h vs 9 h with local infiltration). Powerful nociceptive impulses are generated not only by the surgical procedure itself, but also by the action of proteolytic and inflammatory agents released into the wound tissues. The effect of the latter might be very strong for several hours after surgery. Hence a 9-h effect with bupivacaine infiltration probably offered a better protection than spinal bupivacaine anesthesia, which lasted only 3.5 h.

Thus, our results indicate that infiltration at the surgical incision with a local anesthetic or spinal anesthesia can decrease postoperative pain and that this effect cannot be explained by prolonged presence of a local anesthetic in the body because pain relief was evident in 48 h and, with pressure-induced pain, even 10 days after the surgery. Such long-lasting differences in pain intensity with different types of anesthesia appear to represent more a consequence of the initial anesthetic effect, not an extended pharmacologic action. Recent experimental data indicate that nociceptive impulses may set off a prolonged and widespread increase in spinal cord excitability (15–17). It also has been shown that maximal injury discharge transmitted along C-fiber afferents may even cause transneuronal morphologic changes in the spinal cord (18). Spinal cord hyperexcitability produced by massive nociceptive impulses may be sustained and thus constitute a pathophysiologic mechanism underlying postoperative pain (19). Gen-

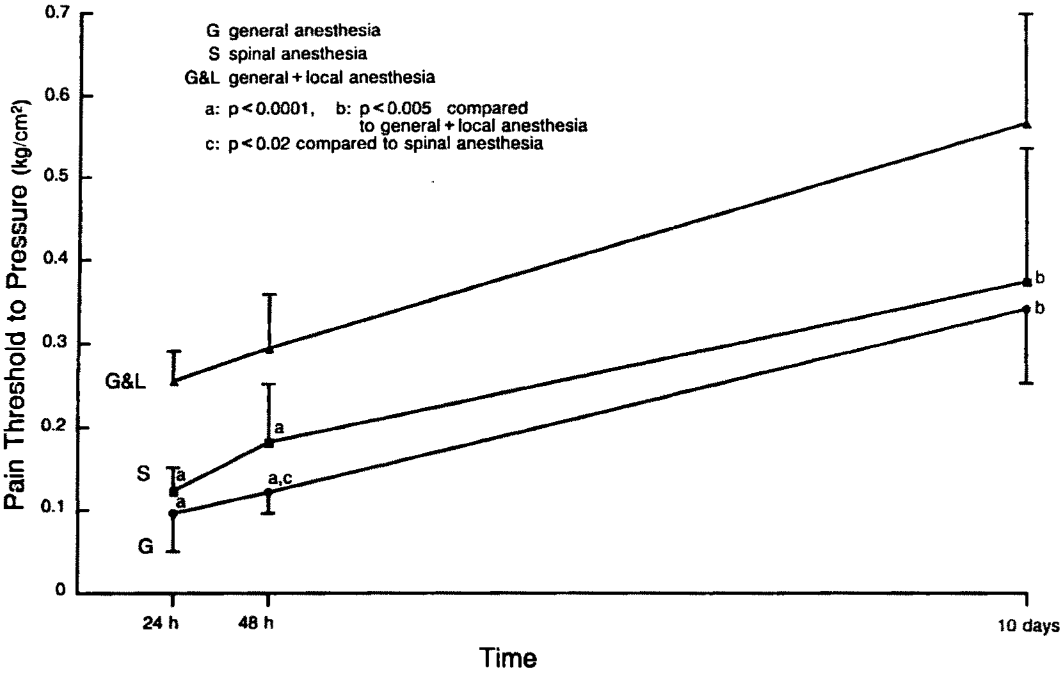

Figure 5. Postoperative pain thresholds to pressure on the surgical wound after three different types of anesthesia (mean ± SEM).

eral anesthesia, in contrast to local infiltration and spinal anesthesia, cannot prevent the transmission of nociceptive impulses from the operative site to the spinal cord. A relatively light level of general anesthesia, which is now a common practice, probably cannot prevent the creation of sustained hyperexcitability in the central nervous system, which most likely is involved in determining the intensity and duration of postoperative pain.

At the beginning of this century, Crile (20) wrote that patients given inhalational anesthesia still need to be protected from stressful surgical stimuli by regional anesthesia; otherwise they might suffer persistent central nervous system changes. Hannington-Kiff (21) has suggested that some patients with persistent pain in the region of previous surgery (despite the absence of any obvious clinical signs) "might have had a scar imprinted on the central nervous system at the time of operation under light general anesthesia" (21). Our data can provide support for this point of view.

In conclusion, postoperative pain after inguinal herniorrhaphy can be significantly decreased if the surgery is performed with local infiltration anesthesia or spinal anesthesia instead of general anesthesia, perhaps because neural blockade prevents nociceptive impulses from entering the central nervous system during and immediately after surgery and thus suppresses formation of the sustained hyperexcitable state in the central nervous system that is responsible for the maintenance of postoperative pain.

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Incidence of Electrocardiographic Changes During Cesarean Delivery Under Regional Anesthesia

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PALMER CM, NORRIS MC, GIUDICI MC, LEIGHTON BL, DESIMONE CA. Incidence of electrocardiographic changes during cesarean delivery under regional anesthesia. Anesth Analg 1990;70:36–43.

Serial electrocardiograms were obtained on 93 healthy ASA physical status I and II term parturients during nonemergent cesarean delivery under regional anesthesia. Electrocardiographic changes occurred in 44 of the 93 patients (47.3%); in 35 of these 44 patients, the changes were characteristic, or suggestive, of myocardial ischemia. Symptoms of chest pain, pressure, and dyspnea occurred in 15 of the 44 patients with electrocardiographic changes; no patient without electrocardiographic change developed symptoms of chest pain, pressure, or dyspnea. Small but statistically significant differences were noted in heart rate, diastolic and systolic arterial pressures, and rate-pressure product between the patients with electrocardiographic changes and those without. The authors speculate that myocardial ischemia is a likely cause of both the electrocardiographic changes seen in these patients and of the symptoms of chest pain and dyspnea that they sometimes experience.

Key Words: ANESTHESIA, OBSTETRIC—cesarean section. ANESTHETIC TECHNIQUES, EPIDURAL—spinal. HEART, MYOCARDIAL ISCHEMIA.

Parturients having regional anesthesia for cesarean delivery frequently complain of chest pain and shortness of breath. The etiology of these symptoms remains unclear; traditional explanations include traction on the peritoneum, exteriorization of the uterus during hysterotomy repair, or retraction by the surgical team. Because of the similarity between parturients' complaints and the complaints offered by symptomatic cardiac patients with myocardial ischemia, we undertook the following study to determine the incidence of another common marker of myocardial ischemia, electrocardiographic changes, during cesarean delivery.

Materials and Methods

Ninety-three ASA physical status I and II term parturients undergoing nonemergent cesarean delivery gave verbal consent to participate in this institutional review board approved study. Any patient with significant coexisting disease (e.g., diabetes mellitus, hypertension) was excluded from the study. All patients received spinal or epidural anesthesia depending on the preferences of the patient and attending anesthesiologist.

Before induction of anesthesia, all patients were prehydrated with 2 L of dextrose-free crystalloid solution. In patients having spinal anesthesia, a 25- or 26-gauge spinal needle was placed at a lower lumbar interspace with the patient in either the sitting or right lateral position. Twelve to fifteen milligrams of hyperbaric 0.75% bupivacaine was injected (obtaining a sensory level of T-4 or higher in all patients), and the patient was placed in the supine horizontal position with left uterine displacement. Patients having lumbar epidural anesthesia had a 20-gauge open-tip catheter placed via an 18-gauge Hustead needle in a lower lumbar interspace. Incremental doses of either 2% lidocaine with epinephrine 1:400,000, 0.5%

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bupivacaine, or 3% 2-chloroprocaine were injected through the catheter to obtain a sensory level to at least T-4. Maternal blood pressure was monitored by an automated blood pressure cuff (Dinamap), oxygen saturation was measured by a Nellcor N-100 pulse oximeter, and heart rate and rhythm were monitored by a Spacelabs model 511 patient monitor. If necessary, 5–10 mg of ephedrine was administered intravenously to maintain maternal systolic blood pressure above 90–100 mm Hg. Oxygen (8–10 L/min) was routinely administered by face mask after induction and until delivery; oxygen was readministered after delivery only if there was evidence of maternal oxygen desaturation, i.e., oxygen saturation of <95%. After delivery, 20 U/L of oxytocin was added to the intravenous infusion.

A Spacelabs model 551 recorder interfaced with the model 511 patient monitor was used to record the maternal electrocardiogram (ECG). The 511 monitor bandwidth is 0.2–75 Hz at −3 dB points. The 551 recorder is a calibrated strip-chart recorder that produces a paper copy of monitored data. Pregelled, self-adhering silver/silver chloride electrodes were placed on the upper extremities bilaterally; lower extremity leads were placed in the midaxillary line at the level of the iliac crests; and the precordial lead was placed beneath the left breast at, or as close as possible to, the V_5 position. Seven leads were recorded (I, II, III, aV_R, aV_L, aV_F, V_5) at the following intervals during the procedure: after induction, skin incision, hysterotomy, delivery, 4 min after delivery, 8 min after delivery, and skin closure. The initial recording (after induction) was obtained as soon as the patient was positioned for surgery on the operating room table, and therefore preceded the attainment of the final sensory level of anesthesia in virtually all cases; additional recordings were made between the latter two times if monitoring indicated any evidence of change. Preoperative 12-lead ECGs were not obtained as they were not considered part of routine preoperative laboratory evaluation of these patients. Any complaints offered by the parturient either spontaneously or in response to nonleading questioning were concurrently recorded, as was maternal blood pressure. The recording clinician was not blinded, but did not attempt interpretation of electrocardiographic recordings.

Electrocardiographic recordings were mounted and numbered serially. A cardiologist (M.C.G.), blinded as to the nature of the procedure and the patient population, analyzed the tracings for the presence and type of any significant changes. ST-T segment depression or elevation of ≥1 mm, change in heart rate or rhythm (other than sinus tachycardia or bradycardia), and changes in conduction were considered significant changes. Less marked changes, i.e., ST-T segment depression or elevation of <1 mm, were noted, although these were not considered significant changes. Because preoperative electrocardiographic recordings were not obtained, the initial strip (after induction) served as baseline for interpretation of subsequent recordings. These findings were subsequently correlated temporally with the observations of symptoms made at operation. Chi-square analysis was used to correlate electrocardiographic changes and anesthetic technique. A contingency table modification of χ^2 was used to analyze the association of symptoms and electrocardiographic changes. Two-way analysis of variance with repeated measurement on one variable (time) was used to determine the statistical significance ($P < 0.05$) of any differences in blood pressure, pulse, or rate-pressure product between women with and without electrocardiographic changes. Significance of comparisons in aggregate hemodynamics was determined by means of a *t*-test for each variable. Group *t*-tests were used to determine differences between retrospectively derived groups.

Table 1. Preoperative Characteristics (*n* = 93)

	Age (yr)	Hemoglobin (mg/dL)	Pulse (beats/min)	Arterial pressure Systolic (mm Hg)	Arterial pressure Diastolic (mm Hg)
Mean	29.5	12.4	83	114	70
Range	19–43	9.6–15.1	60–112	90–168	50–90

Results

Preoperative characteristics of the study population are presented in Table 1. Electrocardiographic changes occurred in 44 of the 93 patients (47.3%). In 35 of these 44 patients, the changes were read as characteristic, or suggestive, of myocardial ischemia. ST-T segment depression (horizontal or downsloping, measured 60 ms after the J point) of ≥1 mm was observed in 26 patients, ST-T segment elevation in four patients, and frequent or multiform premature ventricular contractions in three patients; one patient had simultaneous ST-T segment depression and T-wave inversion, and another had ST-T segment depression and frequent premature ventricular contractions. In an additional nine patients, the ECG showed changes that were considered nondiagnostic; in eight of these nine patients, the changes consisted of distinct ST-T segment depression of slightly less than 1 mm, while in one patient there was T-wave

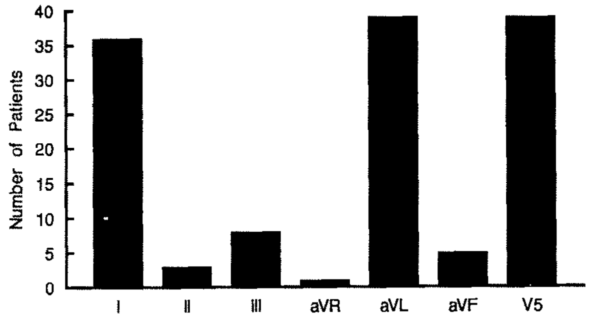

Figure 1. Distribution of electrocardiographic changes by lead (includes all patients with ST-T segment changes).

inversion without other change. Retrospective analysis revealed no statistically significant differences in preoperative variables (age, pulse rate, systolic and diastolic blood pressures, hemoglobin levels) between patients with changes and those without. Leads I, aV_L, and V_5 were most sensitive for detecting changes (see Figure 1). Figure 2 presents examples of some of the changes noted.

The choice of anesthetic technique had no influence on the incidence of electrocardiographic change. Thirty-five of the 74 patients receiving spinal anesthesia and nine of the 19 patients receiving epidural anesthesia developed electrocardiographic changes (P = NS).

Patients with electrocardiographic changes were further analyzed to determine the time of first appearance of the change (Figure 3). Onset of change was fairly evenly distributed between skin incision and 4 min after delivery.

Association of symptoms and electrocardiographic change was statistically significant. Symptoms were offered by 21 of the 93 patients. These symptoms were of three types: those referable to the chest (pain, pressure, dyspnea), which developed in 15 of the 21 patients; nausea and vomiting, in five of the 21; and difficulty swallowing, in one of the 21. Eighteen of these 21 patients had simultaneous changes in their ECG; 14 of these 18 developed electrocardiographic changes characteristic of myocardial ischemia (Table 2). No patient without electrocardiographic change complained of chest pain, pressure, or dyspnea (Table 3). The three remaining patients without electrocardiographic change complained of nausea (two) or difficulty in swallowing (one). Correlation between symptoms and electrocardiographic change was statistically significant ($P < 0.001$).

Electrocardiographic changes and symptoms were transient in all cases; in all patients symptoms resolved and the ECG returned to baseline, or was near resolution, by the conclusion of surgery. Electrocardiographic changes in all cases persisted longer than symptoms. As analysis of ECGs was done retrospectively, no therapeutic intervention was undertaken by clinical staff in response to electrocardiographic changes, nor were follow-up recordings obtained.

Table 4 presents a summary of hemodynamic data. At each point during the procedure, mean values from the group of patients in whom the ECG changed (ECG+) are compared with mean values from the group in whom ECGs remained unchanged (ECG−). Patients with nondiagnostic changes are excluded from this summary. Patients with electrocardiographic changes were likely to have slightly higher heart rates and slightly lower systolic and diastolic arterial pressures. Rate-pressure products were also slightly higher with coincident electrocardiographic changes. The only differences that were statistically significant ($P < 0.05$) are indicated in Table 4. Table 5 compares hemodynamic data obtained at the time of electrocardiographic change (in all patients who had such changes) with all data obtained when ECG was at baseline (in all patients), in an attempt to determine if any absolute level of the measured parameters predisposed to electrocardiographic change. The trend among patients with electrocardiographic change toward higher heart rates and lower systolic and diastolic arterial pressures becomes more apparent in this analysis. Patients with nondiagnostic changes are again excluded. Although the differences between these two groups are slight, they are statistically significant (see P values in Table 5).

Discussion

Complaints of chest pain and dyspnea frequently occur during cesarean delivery under regional anesthesia. The similarity of these complaints to the classical symptoms of myocardial ischemia prompted us to undertake the current study. Nearly half of the patients in this series developed electrocardiographic changes consistent with myocardial ischemia. Further, these changes were consistently noted in lead V_5, the most sensitive lead for the detection of myocardial ischemia (1). Clearly, the design of this study does not allow the diagnosis of myocardial ischemia to be made; given the nature of the observed electrocardiographic changes and the associated symptoms, however, it seems reasonable to speculate that the electrocardiographic changes are ischemic in nature.

Pregnancy is associated with well-defined maternal cardiovascular adaptation; cardiac output increases by 50% over prepregnancy levels, due primarily to an increase in stroke volume (2). With surgical delivery, cardiac output increases still further

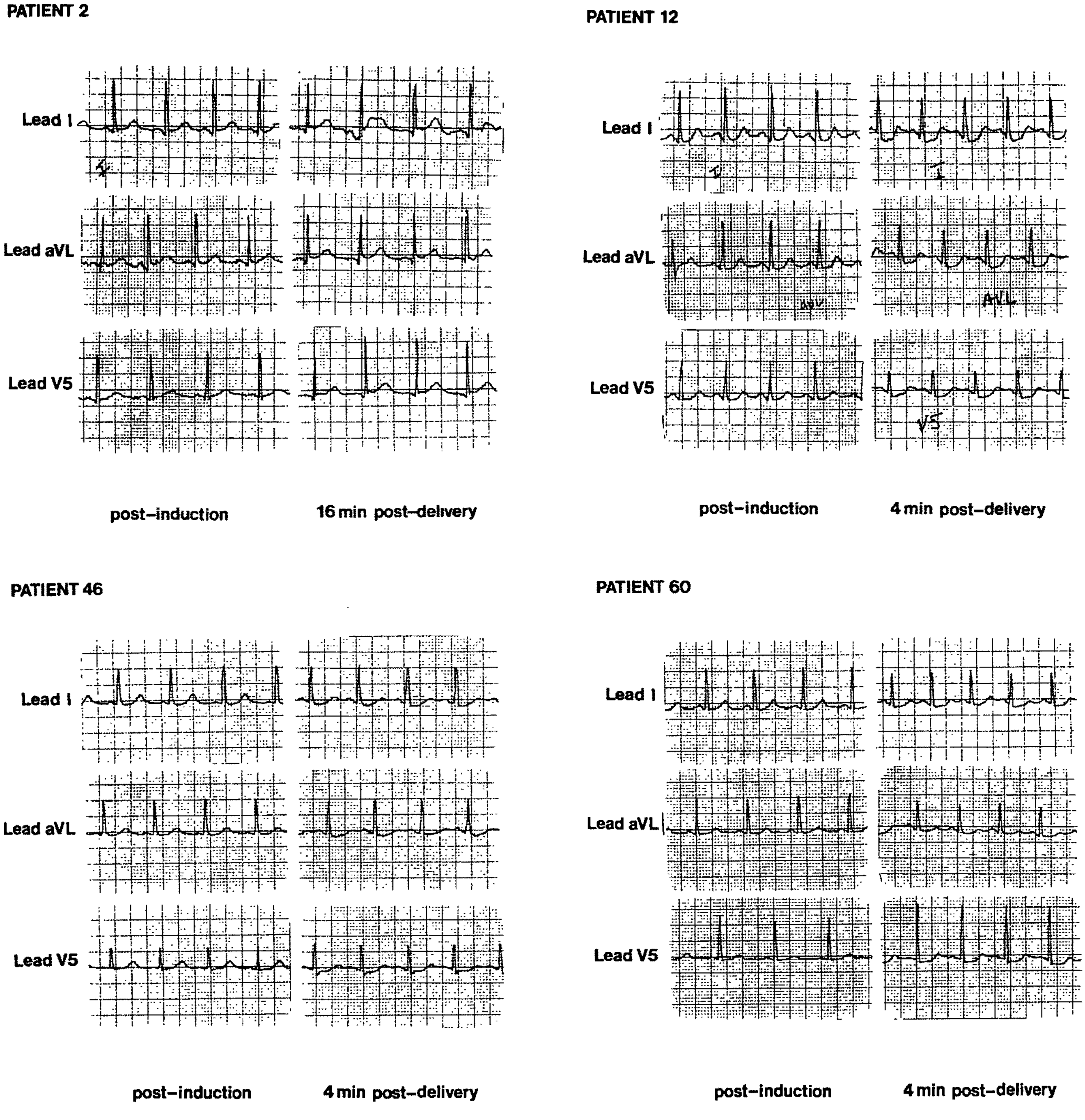

Figure 2. Representative examples of the type of electrocardiographic changes observed. Patient 2 developed ST-T elevation in leads I, aV_L, and V_5 after delivery; patients 12, 46, and 60 had ST-T depression of varying degree in leads I, aV_L, and V_5 after delivery.

due to autotransfusion of blood from the gravid uterus; this is again due largely to an increase in stroke volume (3).

During major regional anesthesia for cesarean delivery, the rapid intravenous administration of 1500–2000 mL of crystalloid (prehydration) is currently recommended to reduce the incidence of maternal hypotension and subsequent uterine hypoperfusion (4,5). The effects of rapidly increasing intravascular volume have been studied in volunteers, in both the presence and absence of sympathetic blockade (6). In healthy, nonpregnant volunteers with an intact sympathetic nervous system, the rapid infusion of 1500 mL of autologous whole blood produced only a small increase in cardiac output and left-ventricular stroke work, with no increase in stroke volume and central blood volume. In the presence of partial sympathetic blockade, however, the same subjects exhibited

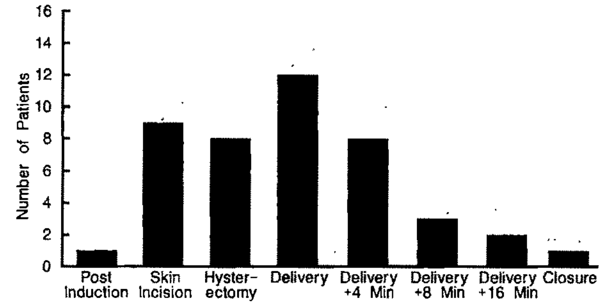

Figure 3. Timing of initial occurrence of electrocardiographic change (includes both patients with significant changes [see text] and patients with nondiagnostic changes, $n = 44$).

Table 2. Symptoms vs Electrocardiographic Change[a]

	Number of patients		
	Symptoms (+)	Symptoms (−)	Total
ECG+[b]	14 (7.9)	21 (27.1)	35
Nondiagnostic	4 (2.0)	5 (7.0)	9
ECG−[b]	3 (11.1)	46 (37.9)	49
Total	21	72	93

[a] "Expected results" (given in parentheses) refer to numbers of patients in each group that would be likely to occur randomly if there were no relation between symptoms and electrocardiographic changes. $P < 0.001$; degrees of freedom = 2 (k − 1, with k = 3).

[b] ECG+ denotes patients with a significant change in electrocardiogram; ECG− denotes patients without significant change in electrocardiogram.

Table 3. Electrocardiographic Changes in Symptomatic Patients

	Number of patients			
	Chest symptoms	Nausea and vomiting	Other	Total
ECG+[a]	11	3	0	14
Nondiagnostic	4	0	0	4
ECG−[a]	0	2	1	3
Total	15	5	1	21

[a] ECG+ denotes patients with a significant change in electrocardiogram; ECG− denotes patients without significant change in electrocardiogram. No statistical analysis has been applied to this data.

marked increases in central blood volume (36%), cardiac output (44%), stroke volume (53%), and left-ventricular stroke work (108%). Sudden hypervolemia in patients with an intact sympathetic nervous system elicits a reflex venodilation that limits the myocardial demands presented by the increased volume load. In the presence of sympathetic blockade, sudden hypervolemia markedly increases myocardial work and myocardial oxygen demand. This was seen in a study by Nishimura et al. (7) who measured central pressures and ventricular function during rapid colloid infusion in nonpregnant patients with "high" (>T-4) epidural anesthesia. They found significant increases in pulmonary arterial, pulmonary capillary wedge, and central venous pressures, as well as in stroke volume index; further, they observed the appearance of large V waves in the pulmonary arterial and pulmonary capillary wedge pressure tracings, consistent with overdistention of the ventricle. They concluded that high epidural blockade can depress cardiac performance by decreasing contractility and limiting the compensatory response to expansion of the ventricles by volume infusion.

As already noted above, pregnancy places increased demands on the myocardium and thereby increases myocardial oxygen demand. Two distinct effects of regional anesthetics can be identified as having a potentially adverse effect on myocardial oxygen demand and supply. At cesarean delivery, the acute hypervolemia induced by prehydration and autotransfusion from the uterus may, in the presence of sympathetic blockade, place excessive demands on the myocardium causing transient increases in left ventricular end-diastolic volume (and pressure), thereby increasing myocardial oxygen demand. Concurrently, a sympathectomy-induced decrease in diastolic arterial pressure decreases coronary perfusion pressure and impairs myocardial oxygen supply. The net effect of this increased demand and decreased supply may be the occurrence of subendocardial ischemia, with subsequent symptoms and electrocardiographic changes.

ST-T segment changes are a commonly used marker of myocardial ischemia in the presence of coronary artery disease (CAD). It would be unreasonable to suspect that nearly half of the young, healthy women in the present study had significant CAD. Although it is difficult to estimate the incidence of significant CAD in an asymptomatic population, even the most pessimistic estimate would put the incidence of CAD in women this age well below 5%, probably below 1% (8,9). Several studies have addressed the issue of the "specificity" of exercise-induced changes in the ST segment for significant CAD in women, resulting in estimates of specificity ranging from 63% to 92% (10); such studies have led to the conclusion that the incidence of "false-positive" electrocardiographic changes is higher in women than men. Extrapolation from such reports to the present study may be misleading in that the prior reports have attempted to correlate ST segment response with clinically significant CAD; clearly, the parturients in this study *did not* have significant CAD.

Can myocardial ischemia occur in the absence of

Table 4. Comparative Hemodynamics[a]

	Skin incision	Hysterectomy	Delivery	Delivery + 4 min	Delivery + 8 min	Delivery + 16 min	Closure
Heart rate (beats/min)							
–	92	88	97	97[b]	95	96	91
	(1.9)	(1.8)	(2.0)	(1.8)	(2.1)	(2.6)	(1.6)
+	101	92	104	106[b]	99	103	96
	(5.3)	(3.4)	(3.7)	(3.0)	(4.1)	(5.1)	(4.5)
Systolic presssure (mm Hg)							
–	108	113	112[b]	104	108	102	108
	(1.5)	(1.8)	(1.9)	(2.1)	(2.5)	(4.0)	(1.8)
+	106	108	104[b]	102	102	104	111
	(2.7)	(4.1)	(2.5)	(3.3)	(3.4)	(2.2)	(4.0)
Diastolic pressure (mm Hg)							
–	54	57[b]	55[b]	50[b]	52[b]	51	56
	(0.9)	(1.2)	(1.4)	(1.5)	(1.5)	(1.8)	(1.8)
+	49	51[b]	46[b]	44[b]	45[b]	49	50
	(1.2)	(2.2)	(1.4)	(1.8)	(1.8)	(2.2)	(2.3)
Rate-pressure product							
–	10,015	9,819	10,561	10,122	10,222	9,819	9,817
	(258.6)	(234.2)	(302.7)	(276.4)	(323.1)	(478.8)	(240.5)
+	10,586	9,931	10,832	10,832	10,194	10,650	10,664
	(548.2)	(587.0)	(494.6)	(557.9)	(567.1)	(579.2)	(633.6)

Values are mean, standard error of the mean is given in parentheses.

[a] For purposes of this analysis, mean values from patients whose electrocardiogram demonstrated significant change (+) ($n = 35$) at each time are compared with mean values from patients without electrocardiographic change (–) ($n = 49$) at the same point in the procedure. See text for complete details.

[b] Statistically significant differences ($P < 0.05$).

Table 5. Aggregate Comparison of Hemodynamics

	Systolic pressure	Diastolic pressure	Heart rate	Rate-pressure product
ECG+ ($n = 105$)				
Mean	105	47	100	10,539
SEM	1.3	0.8	1.6	214.1
ECG– ($n = 335$)				
Mean	109	54	93	10,065
SEM	0.8	0.5	0.8	108.2
P value	0.013	<0.001	<0.001	0.038

n, number of observations; ECG+ denotes observations made at a point where the electrocardiogram was significantly changed, as noted in text; ECG– denotes observation made while electrocardiogram was unchanged or at baseline.

CAD, and are ST segment changes a valid marker of ischemia in the absence of CAD? The answer to these questions would appear to be "yes." Myocardial infarction in the peripartum period is the subject of numerous reports and, interestingly, is often found to be associated with normal coronary arteries (11–16). Although the proposed mechanism of such injury is coronary artery spasm, ergovine provocation has failed to document this when attempted (17). Nevertheless, it appears that significant myocardial ischemia *can* occur in this population in the absence of CAD.

Other factors have been associated with false-positive electrocardiographic changes in patients without CAD. Hyperventilation can cause T-wave inversion in some patients. Mitral valve prolapse has also been associated with false-positive electrocardiographic changes in some young women (18). The incidence of undiagnosed mitral valve prolapse in this population could not reasonably be expected to exceed 6%–7%, however (19). Electrolyte imbalance can also cause electrocardiographic changes; although plasma electrolyte levels were not measured in the patients in this study, it seems unlikely that significant derangements occurred so frequently without other signs or symptoms. Coronary vasospasm can cause ST-T segment changes in otherwise normal patients; again, although the present study was not designed to detect vasospasm, there is no evidence that it is so frequent in this population, nor does it appear to be a causative factor in parturients who suffer myocardial infarction (17).

The role of ancillary drugs in the possible genesis of the observed electrocardiographic changes must also be considered. Ephedrine is a sympathomimetic that stimulates both α- and β-adrenergic receptors, and the release of norepinephrine from sympathetic neurons (20). It is widely used in obstetrics to treat and prevent hypotension during regional anesthesia, and was used intravenously in this series to treat hypotension when it occurred; unfortunately, the timing of administration was not recorded, and possible relation to observed electrocardiographic changes is therefore a matter of speculation. Ephedrine elevates both systolic and diastolic pressures in humans, mainly through cardiac stimulation; heart rate, myocardial contractility, and cardiac output all increase if venous return is adequate. Such effects would increase myocardial oxygen demand and could aggravate myocardial ischemia (and resultant electrocardiographic changes) if present. If ischemia occurs in part due to decreased coronary perfusion, via the mechanism proposed above, ephedrine may decrease ischemia by increasing diastolic arterial pressure. Elucidation of this effect awaits further study.

Oxytocin is a neurohypophyseal hormone that stimulates the contraction of uterine smooth muscle and is commonly administered after cesarean delivery, as it was to all patients in this series. It has a direct relaxing effect on vascular smooth muscle, and can cause a decrease in both systolic and diastolic blood pressures. In doses commonly used in obstetrics, and employed in this series, marked alterations in blood pressure are uncommon (21). Intracoronary administration of oxytocin may produce vasoconstriction of coronary arteries (22), but it is unlikely that a concentration sufficient to produce such an effect was achieved in this series. Oxytocin may have contributed to the observed electrocardiographic changes by its systemic blood pressure effects, if the mechanism of myocardial ischemia proposed above is accurate; clearly, direct coronary vasoconstriction due to oxytocin could contribute to the electrocardiographic changes. Although impossible to prove from the data collected in this series, we believe that the time of occurrence of most of the electrocardiographic changes (i.e., before oxytocin administration) makes oxytocin an unlikely cause or contributor (Figure 3).

Sedatives are sometimes administered as an adjunct to regional anesthesia for cesarean delivery. Intravenous fentanyl was employed as an analgesic after delivery in <10% of the patients in this series in doses of 50–100 μg (0.6–1.4 μg/kg). Doses in this range are generally associated with decreased myocardial oxygen consumption, left ventricular end diastolic pressure, and cardiac work. Actual effects in any given patient are quite variable, however, due to effects on heart rate and blood pressure (23).

Cesarean deliveries under general anesthesia were not included in this study. Parturients receiving general anesthesia are not routinely prehydrated and do not have the sympathectomy associated with high levels of regional anesthesia (24). If acute plasma volume expansion and sypathectomy do contribute to electrocardiographic changes as hypothesized above, electrocardiographic changes would not be expected to occur under general anesthesia. Similarly, regional anesthesia with smaller volumes of prehydration and greater reliance on vasopressors (ephedrine) would also be expected to have a lower incidence of electrocardiographic changes. These areas remain to be investigated.

A report by Malinow et al. (25) found precordial Doppler evidence of venous air emboli in 52% of patients undergoing cesarean delivery under regional anesthesia. Further, they demonstrated significant correlation between patient complaints of chest pain and the Doppler changes. Unfortunately, we did not attempt to correlate electrocardiographic changes with precordial Doppler findings. Malinow et al. state in their report that small air emboli can cause complaints of dyspnea and chest pain, but there is little evidence to support this contention. Studies of venous air emboli in the anesthesia literature commonly involve patients under general anesthesia, and therefore patient complaints are unavailable. Intracardiac venous air emboli do commonly occur in subjects with decompression sickness, however, also known as "the bends." None of the numerous studies of decompression sickness report chest pain or dyspnea even in the face of continuous showers of intracardiac air (26–28). Indeed, precordial Doppler monitoring is used to detect preclinical decompression sickness in asymptomatic patients.

In summary, we conclude that significant electrocardiographic changes occur frequently in term parturients during cesarean delivery, and that these changes are of the type commonly associated with myocardial ischemia. A review of both the specificity of the electrocardiographic response in this population and accepted causes of both positive and false-positive electrocardiographic changes fails to provide an adequate explanation for the high incidence of electrocardiographic changes that we observed. Although the design of this study clearly has deficiencies and limitations, we believe that the association of the electrocardiographic changes and chest pain make it reasonable to speculate that myocardial ischemia may be their cause. We offer one possible explanation for the occurrence of such ischemia. Clearly, more work needs to be done in this area to elucidate further the nature of these electrocardiographic changes and consequences for anesthetic management.

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Comparison of Hemodynamic Changes Induced by Adenosine Monophosphate and Sodium Nitroprusside Alone and During Dopamine Infusion in the Anesthetized Dog

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FINEGAN BA, CHEN H-J, SINGH YN, CLANACHAN AS. Comparison of hemodynamic changes induced by adenosine monophosphate and sodium nitroprusside alone and during dopamine infusion in the anesthetized dog. Anesth Analg 1990;70:44–52.

Adenosine receptor stimulation, such as by adenosine monophosphate (AMP), elicits systemic vasodilation that may be useful to control cardiac afterload during treatment of acute low-output cardiac failure. This study compared the hemodynamic effects of graded doses of sodium nitroprusside (SNP) with those of AMP when infused alone or in combination with the positive inotropic agent dopamine (DA) in anesthetized dogs. Both SNP (2–25 $\mu g \cdot kg^{-1} \cdot min^{-1}$) and AMP (200–2500 $\mu g \cdot kg^{-1} \cdot min^{-1}$) were effective vasodilators and reduced systemic vascular resistance and arterial pressure in a dose-dependent manner. Heart rate and cardiac index were increased by both agents. When compared at dosages that caused similar decreases in arterial pressure, cardiac index was increased more by AMP than by SNP. Also, AMP-induced vasodilation was associated with less tachyphylaxis. Sodium nitroprusside and AMP, at the dosages used, did not depress atrioventricular nodal conduction or antagonize DA-induced increases in renal blood flow. At equivalent decreases in mean arterial pressure, the increase from baseline in cardiac and stroke indices observed with AMP alone was further increased by the concomitant administration of DA. These results suggest that AMP and DA-AMP may offer significant advantages over SNP or DA-SNP in situations where elevation of cardiac output and reduction in afterload are required.

Key Words: ANESTHETIC TECHNIQUES, HYPOTENSIVE—adenosine, nitroprusside. SYMPATHETIC NERVOUS SYSTEM, PHARMACOLOGY—dopamine.

A reduction in impedance to left ventricular ejection (afterload) of the failing ventricle improves myocardial efficiency, decreases myocardial energy expenditure, and redirects energy into ejecting blood rather than in developing pressure (1). Sodium nitroprusside (SNP) and glyceryl trinitrate (GTN) are useful in reducing afterload in acute cardiac failure.

The failing heart has decreased contractility which can be enhanced by positive inotropic agents such as dopamine (DA). These drugs increase contractility, but at the expense of increases in afterload and myocardial oxygen utilization. The combination of an inotrope with a vasodilator has been demonstrated to be superior to either drug used alone, in both acute (2) and chronic heart failure (3).

Adenosine, an endogenous nucleoside with predominantly arterial vasodilating properties, is used clinically to produce controlled hypotension during anesthesia (4) and in terminating supraventricular tachydysrythmias (5). Adenosine and its nucleotides depress atrioventricular (AV) nodal conduction and inhibit atrial and ventricular automaticity by stimulating adenosine A_1-receptors in the myocardium (6). Stimulation of adenosine A_2-receptors in the arterioles causes smooth muscle relaxation and vasodilation (7). In addition, adenosine and its analogues inhibit the renin-angiotensin system (8). Consequently, adenosine and its analogues may be alternatives to SNP and GTN in the treatment of acute low cardiac output states. Adenosine receptor stimulation may attenuate the increases in heart rate and atrial

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and ventricular automaticity that are adverse reactions of positive inotropic drugs, such as DA.

The objective of this study was to compare separately the hemodynamic properties of adenosine monophosphate (AMP), a soluble adenosine prodrug, with SNP alone and during infusion of the positive inotropic drug DA in normal anesthetized dogs and to assess the effects of the drug combinations on AV conduction.

Methods

Approval for animal use in this study was granted by the Animal Care Committee of the University of Alberta. Experiments were performed on mongrel dogs ($n = 15$) of either gender, weighing between 11 and 18 kg (mean 13.7 kg). Anesthesia was induced with pentobarbital (30 mg/kg) and after intubation with a cuffed endotracheal tube, ventilation with an air-oxygen mixture was provided by a Harvard Apparatus Co. (South Natick, Mass.) respirator controlled to maintain normal carbon dioxide (CO_2) tensions. Acidosis was corrected when required by sodium bicarbonate. End-tidal CO_2 (Beckman Instruments, Inc., Fullerton, Calif.; LB2 analyzer) was monitored continuously. Anesthesia was maintained by a constant infusion (4 $mL \cdot kg^{-1} \cdot h^{-1}$) of fentanyl (20 $\mu g \cdot kg^{-1} \cdot h^{-1}$), pentobarbital (3 $mg \cdot kg^{-1} \cdot h^{-1}$), and pancuronium (100 $\mu g \cdot kg^{-1} \cdot h^{-1}$) in normal saline. Catheters were placed in the femoral artery for direct measurement of arterial pressure and for arterial blood sampling, and in a femoral vein for drug administration. A jugular vein was cannulated to allow passage of a pulmonary artery catheter (Swan Ganz) and for fluid loading (10 mL/kg of 6% Dextran-70 in normal saline) and anesthetic infusion. Electrocardiogram tracings, heart rate, and arterial, central venous, and pulmonary artery pressures were measured and continuously recorded (Grass Instrument Co., Quincy, Mass.; model 7 polygraph). Cardiac output was determined as required by thermodilution (Edwards cardiac output computer), each value being an average of four individual determinations. Temperature was maintained between 37° and 38°C by a warming blanket. Arterial blood samples were taken at appropriate times for determination of blood gas tensions. Infusion of test drugs was by a triple-lumen catheter placed in a femoral vein, infusion rates being controlled by Harvard infusion pumps. Initial baseline values were recorded 30 min following instrumentation and repeated every 10 min for 30 min to evaluate the stability of the experimental preparation. Two series of experiments were performed. In series A ($n = 7$) the objective was to evaluate dose-response relationships for AMP or SNP alone or in the presence of DA (5 $\mu g \cdot kg^{-1} \cdot min^{-1}$). Renal blood flow was measured by an electromagnetic flow probe (Gould SP2202, Gould Inc., Oxnard, Calif.) placed on the left renal artery and recorded on the polygraph recorder. In each animal graded doses of AMP (200, 500, 1000, and 2500 $\mu g \cdot kg^{-1} \cdot min^{-1}$) and SNP (2, 5, 10, and 25 $\mu g \cdot kg^{-1} \cdot min^{-1}$) were infused in a randomized order. Values were recorded after 10 min of drug infusion at each dose level. Between each vasodilator dose, 15 min was allowed to permit values to return to baseline. The infusions were repeated in the presence of DA (5 $\mu g \cdot kg^{-1} \cdot min^{-1}$). If a dose of vasodilator decreased mean arterial pressure (MAP) below 75 mm Hg, no further doses were administered. This allowed comparison of values within the autoregulatory range and maintained the stability of the experimental model.

Table 1. Control Cardiovascular Parameters

Parameter	Mean ± SEM	Units
Heart rate	80 ± 2	beats/min
Systolic arterial pressure	145 ± 6	mm Hg
Diastolic arterial pressure	98 ± 3	mm Hg
Mean arterial pressure	114 ± 4	mm Hg
Systolic pulmonary pressure	25 ± 2	mm Hg
Diastolic pulmonary pressure	11 ± 1	mm Hg
Mean pulmonary pressure	15 ± 1	mm Hg
Pulmonary capillary wedge pressure	11 ± 1	mm Hg
Central venous pressure	5.9 ± 0.5	mm Hg
Renal blood flow	140 ± 29	mL/min
Cardiac index	2.84 ± 0.06	$L \cdot min^{-1} \cdot m^{-2}$
Stroke index	35.6 ± 0.6	mL/m^2
Systemic vascular resistance	4550 ± 160	$dyne \cdot s \cdot cm^{-5}$
Pulmonary vascular resistance	201 ± 33	$dyne \cdot s \cdot cm^{-5}$
Atrioventricular conduction time	141 ± 7	ms

In protocol B ($n = 8$) the objective was to reduce MAP to 80 mm Hg by AMP or SNP during continuous low-dose DA infusion (5 $\mu g \cdot kg^{-1} \cdot min^{-1}$) and to assess the effect of these drug combinations on AV conduction times and on ease and stability of MAP control. A bipolar pacing electrode was placed under fluoroscopic guidance into the right atrium via a femoral vein. Fifteen-second periods of stimulation (3 Hz) were applied (Grass stimulator model SM6) and stimulus artifact–R intervals were averaged from five consecutive cycles using high-speed electrocardiogram recordings (100 mm/s). Hemodynamic and AV conduction values were recorded during the baseline period, after 10 min of DA infusion, and during the DA/AMP and DA/SNP combinations at the target MAP of 80 mm Hg. Adenosine monophosphate and SNP were infused in a random order in a dose sufficient to maintain MAP at 80 mm Hg for 10 min. After

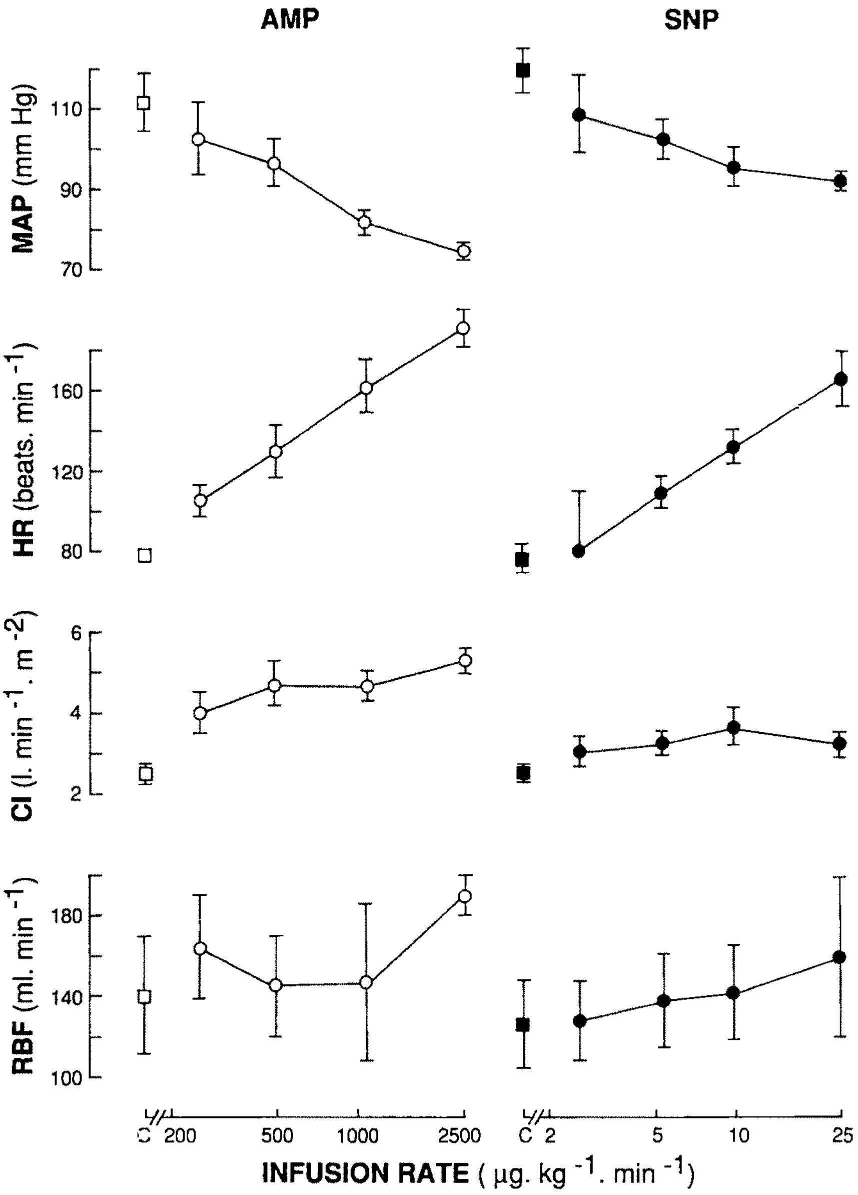


Figure 1. Effects of graded intravenous infusions of AMP (200–2500 $\mu g \cdot kg^{-1} \cdot min^{-1}$, ○) and SNP (2–25 $\mu g \cdot kg^{-1} \cdot min^{-1}$, ●) on MAP, heart rate (HR), cardiac index (CI), and renal blood flow (RBF) in anesthetized dogs. Baseline, prevasodilator values for the AMP (□) and SNP (■) groups are also shown. Points represent the mean ± SEM ($n = 7$).

each drug combination, DA alone was continued and the parameters were allowed to return to prevasodilator values.

Mean pressures, stroke index, and systemic, renal, and pulmonary vascular resistances were calculated using standard equations (9). Data are presented as mean ± SEM. The significance of the differences between hemodynamic variables was determined using Student's paired *t*-test and analysis of variance and judged to be statistically significant when $P < 0.05$.

Results

Anesthesia in dogs with fentanyl-pentobarbital infusions provided a stable hemodynamic state (Table 1) with heart rates similar to those in conscious animals (about 80–90 beats/min).

Adenosine Monophosphate and Sodium Nitroprusside Dose Responses

Both drugs reduced systemic arterial pressure in a dose-dependent manner (Figure 1). This effect was rapid in onset and was well maintained in the case of AMP. The SNP-induced hypotension was associated with tachyphylaxis and at the end of every 10-min infusion period, MAP had recovered by 10%–15%. After discontinuation of AMP or SNP infusion, arterial pressure recovered rapidly (1–2 min). With each vasodilator, there was a significant ($P < 0.001$) in-

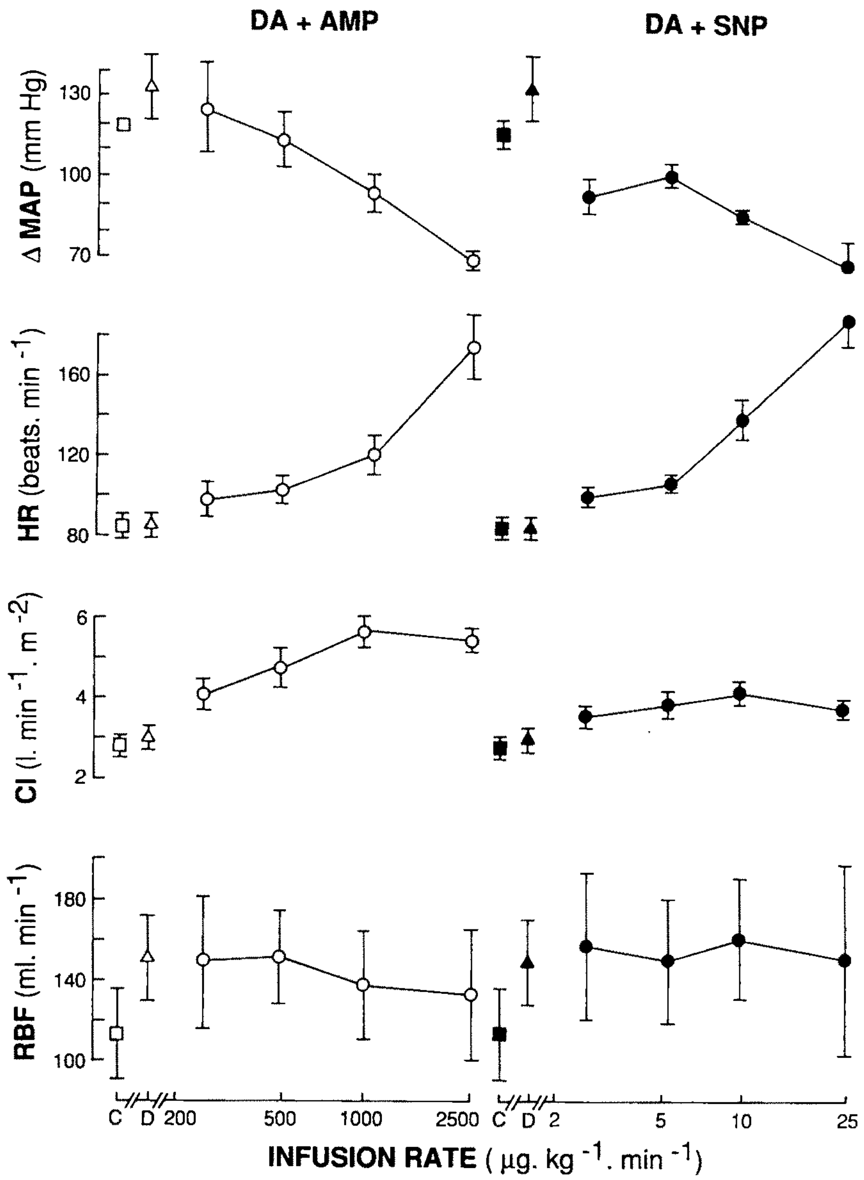


Figure 2. Effects of graded intravenous infusions of DA (5 μg·kg^{-1}·min^{-1}) alone (△, ▲) and in combination with AMP (200–2500 μg·kg^{-1}·min^{-1}, ○) or SNP (2–25 μg·kg^{-1}·min^{-1}, ●) on MAP, heart rate (HR), cardiac index (CI), and renal blood flow (RBF) in anesthetized dogs. Baseline, prevasodilator values for the AMP (□) and SNP (■) groups are also shown. Points represent the mean ± SEM ($n = 7$).

crease in heart rate (Figure 1). Cardiac index was also significantly increased by AMP ($P < 0.001$) and SNP ($P < 0.01$), whereas renal blood flow was not significantly altered (Figure 1) by either vasodilator.

Dopamine (5 μg·kg^{-1}·min^{-1}) alone (Figure 2) had minimal effects on MAP and cardiac index. The vasodilators possessed a similar profile of activity when administered in combination with DA (Figure 2). Dopamine alone also increased renal blood flow by 30% ± 5% ($P < 0.01$), but this increase was not affected by the simultaneous infusion of AMP or SNP (Figure 2). To compare the effects of AMP and SNP at equieffective dosages, plots were constructed showing the change in a particular parameter against the change in MAP induced by each dose of each vasodilator (Figures 3 and 4). Adenosine monophosphate increased cardiac index more than did SNP ($P < 0.01$). This greater elevation in cardiac function was demonstrable in the absence or presence of DA infusion, although the addition of DA resulted in greater increases in cardiac index and stroke index with smaller alterations in arterial pressure (Figure 3). Interestingly, stroke index increased during AMP/DA combinations whereas equieffective vasodilator dosages of SNP/DA decreased stroke index (Figure 3). Systemic, pulmonary, and renal vascular resistance decreased with each vasodilator (Figure 4).

Although pulmonary vascular resistance was reduced by each vasodilator, pulmonary artery pressure was not decreased uniformly by AMP. At low

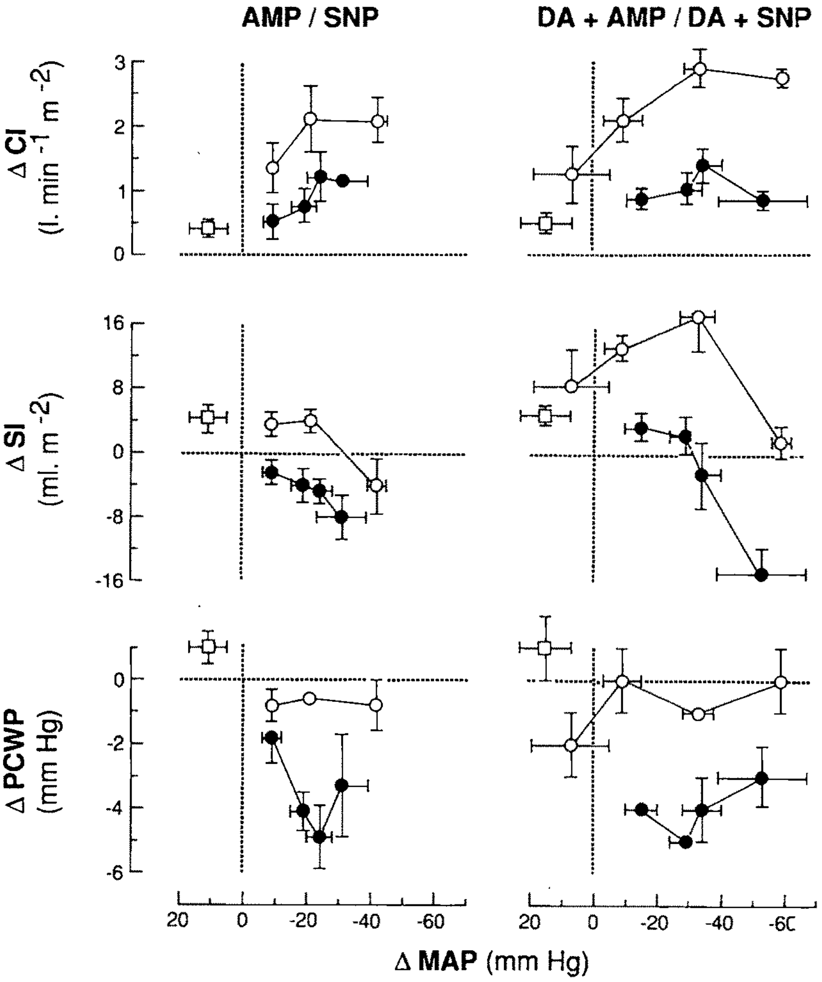


Figure 3. Effects of changes in MAP (ΔMAP) induced by AMP (○) or SNP (●) alone or in combination with DA (5 $\mu g \cdot kg^{-1} \cdot min^{-1}$) on cardiac index (ΔCI), pulmonary capillary wedge pressure (ΔPCWP), and stroke index (ΔSI). The effects of DA alone (□) are also shown. Points are mean ± SEM ($n = 7$).

doses (Figures 3 and 4) pulmonary vascular resistance was maintained at baseline values despite an increase in cardiac index.

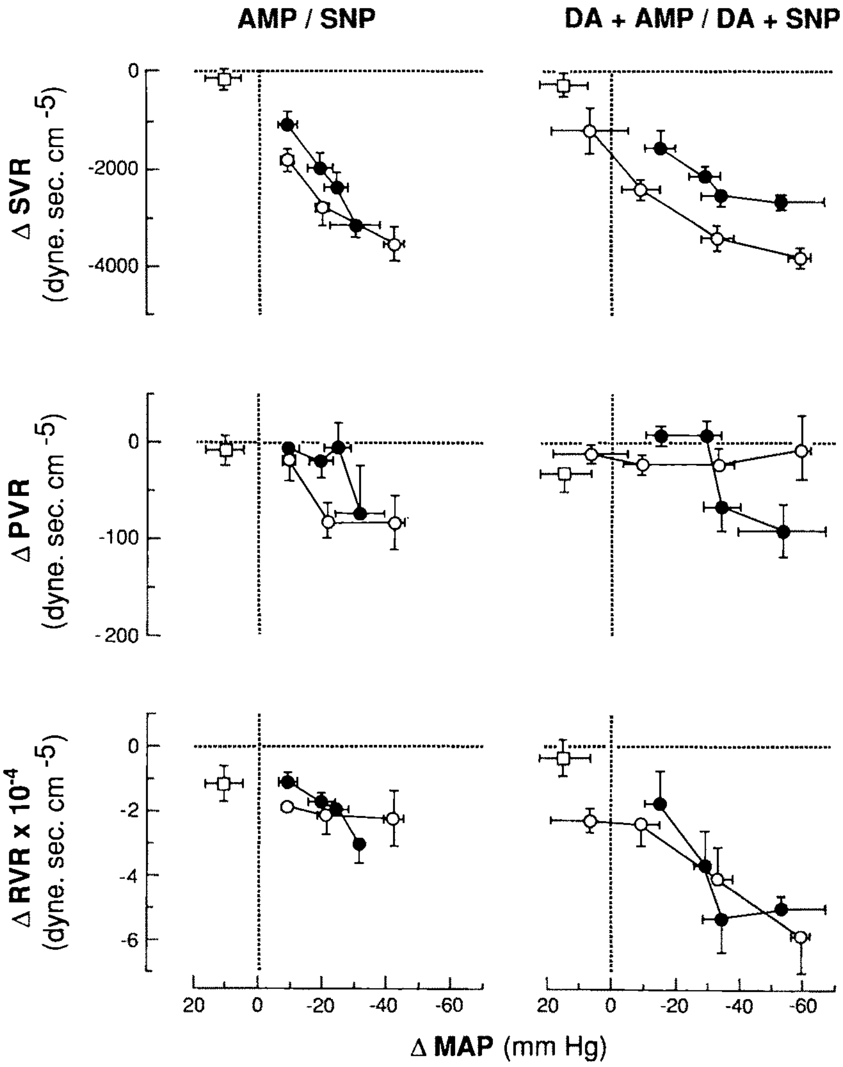
Steady-State Responses at Mean Arterial Pressure of 80 mm Hg

When administered during continuous DA infusion (5 $\mu g \cdot kg^{-1} \cdot min^{-1}$), AMP and SNP reduced systemic and pulmonary vascular resistances and effectively reduced MAP to the targeted value of 80 mm Hg (Figure 5). The effects of SNP infusion were more difficult to maintain and continual adjustment of infusion rate was required. In contrast, AMP was not associated with the development of tachyphylaxis. Mean infusion rates required to maintain a MAP of 80 mm Hg after a 10-min infusion were 1.1 $mg \cdot kg^{-1} \cdot min^{-1}$ for AMP and 0.014 $mg \cdot kg^{-1} \cdot min^{-1}$ for SNP. Although MAP was reduced to a similar extent, DA/AMP increased cardiac index significantly ($P < 0.01$) more than DA/SNP did (Figure 6). Stroke index was increased by AMP ($P < 0.05$), but depressed by SNP ($P < 0.01$), the latter probably due to the significantly ($P < 0.01$) greater reflex tachycardia. Although pulmonary vascular resistance was reduced by each vasodilator, pulmonary artery pressure was increased ($P < 0.05$) by DA/AMP. The AV nodal conduction interval was reduced by a similar degree by each vasodilator (Figure 6). No periods of drug-induced AV nodal block were observed.

Discussion

This study has compared the hemodynamic effects of AMP with SNP when infused alone, or in combination with DA, in normal anesthetized dogs. As expected (10), SNP was an effective vasodilator and reduced systemic vascular resistance and arterial pressure in a dose-dependent manner. Adenosine monophosphate was also an effective vasodilator although ~100-fold less potent than SNP. Heart rate

Figure 4. Effects of changes in MAP (ΔMAP) induced by AMP (○) or SNP (●) alone or in combination with DA (5 $\mu g \cdot kg^{-1} \cdot min^{-1}$) on systemic (ΔSVR), renal (ΔRVR), and pulmonary (ΔPVR) vascular resistance. The effects of DA alone (□) are also shown. Points are mean ± SEM ($n = 7$).



and cardiac index were increased by both AMP and SNP. When compared at infusion rates that caused equivalent decreases in MAP, AMP increased cardiac index to a significantly greater extent than SNP. This occurred with or without DA infusion. This suggests that AMP may be preferable to SNP as an afterload reducer in drug combinations for the management of low output cardiac failure.

The cardiovascular effects of adenosine and its nucleotides have been extensively studied in animals and humans (11). Although afterload reduction that would contribute to an enhancement of cardiac index could be induced by almost any vasodilator, adenosine receptor agonists have not hitherto been evaluated in vasodilator-catecholamine combinations. High-affinity A_1-receptor stimulation mediates cardiac depression, including negative chronotropic and inotropic effects and blockade of AV nodal conduction. Consequently, it might be expected that at plasma concentrations that elicit vasodilation by low-affinity A_2-adenosine receptors, significant and detrimental A_1-mediated cardiac depression would also occur. However, no adverse cardiac effects of AMP were observed in this study. The AV nodal conduction times decreased during both SNP and AMP administration and during combination infusions with DA. This facilitation of conduction was likely mediated via reflex sympathetic activation. Nevertheless, when arterial pressure was reduced to the same level, heart rates were less during vasodilation induced by AMP. This attenuation of reflex tachycardia is probably mediated by a direct effect on the sinoatrial (SA) node because adenosine A_1-receptor stimulation inhibits SA nodal depolarization (12). Also, it has been noted previously that reflex tachycardia during hypotension induced by adenosine is less than that induced by glyceryl trinitrate (13) or SNP (14). Although no direct assessment of cardiac contractility was per-

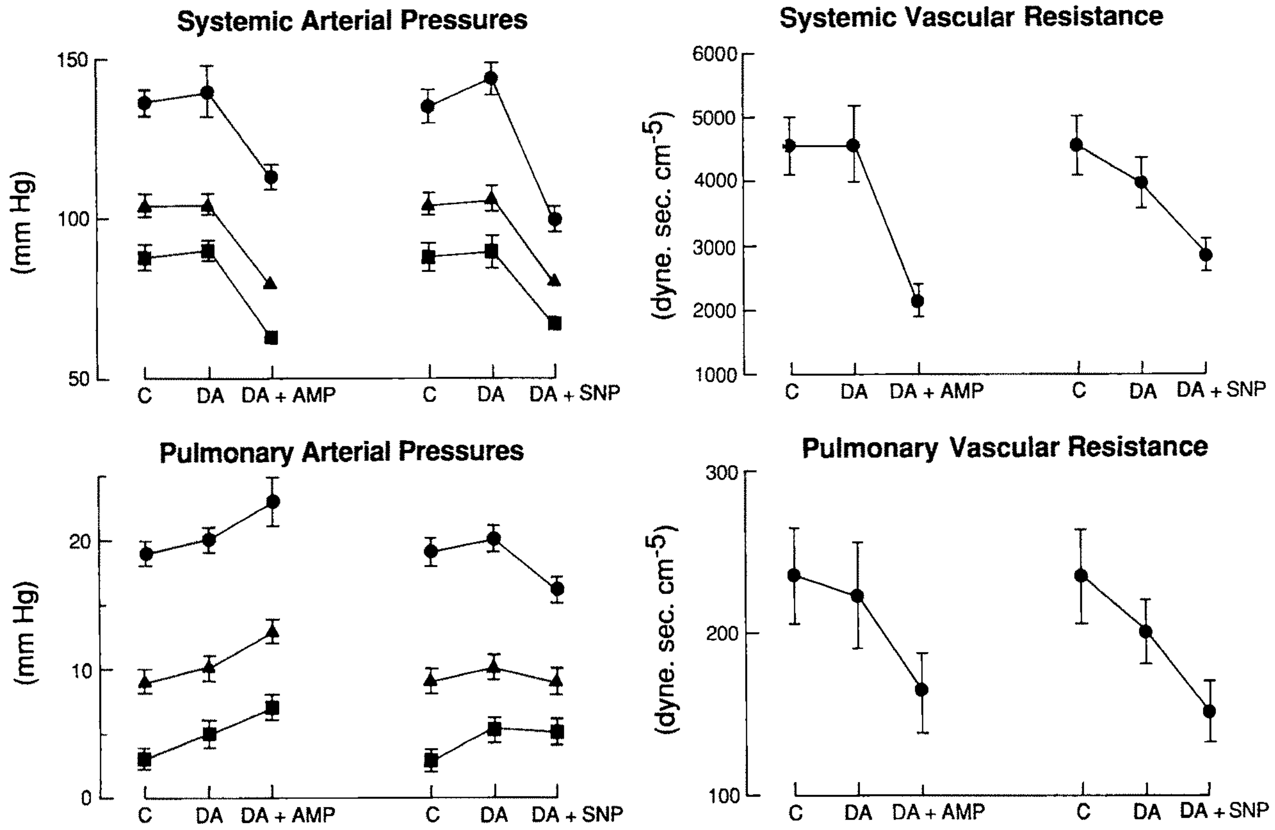


Figure 5. Effects of reducing MAP to 80 mm Hg by AMP or SNP during DA infusion (5 $\mu g \cdot kg^{-1} \cdot min^{-1}$) on systemic and pulmonary systolic (●), mean (▲), and diastolic (■) pressures and on systemic and pulmonary vascular resistance of anesthetized dogs. Values are given for baseline (C), DA alone (DA), and the combinations of DA with AMP (DA + AMP) or DA with SNP (DA + SNP). Points represent the mean ± SEM (n = 8).

formed in this series of experiments, the greater elevation in cardiac output induced by AMP suggests an absence of significant myocardial depression.

The significantly greater increase in cardiac index induced by AMP than by SNP may be due to several factors. First, AMP is a selective arterial vasodilator whereas SNP causes both arterial and venous dilation that leads to a decrease in ventricular filling pressures. Filling pressures were maintained (pulmonary capillary wedge pressure >8 mm Hg) before vasodilator infusions but no compensation for drug-induced changes in preload, e.g., by additional fluid loading, was made. Second, reflex tachycardia was attenuated by AMP, resulting in more efficient ventricular function. Also, AMP is metabolized to adenosine that is rapidly deaminated by adenosine deaminase to yield inosine. The latter is a positive inotropic agent (15), but infusion rates (up to 5 $mg \cdot kg^{-1} \cdot min^{-1}$) that are far in excess of those used in the present study are required to cause significant cardiac stimulation. However, if the conversion of AMP to inosine occurred predominantly in the myocardium, sufficient inosine may have been produced locally to cause a positive inotropic action. Under certain conditions, adenosine per se may possess positive inotropic properties (16). Adenosine is also considered to have antiadrenergic effects in the heart by an attenuation of the catecholamine-induced elevation of cyclic AMP (17). Antagonism of DA-induced cardiac stimulation was not observed in this study and this supports more detailed investigations that demonstrated an absence of adenosine-catecholamine antagonism in the canine heart (18).

The maintenance of pulmonary vascular resistance at baseline values in the face of an increased cardiac index during lower dose AMP infusion and AMP/DA infusion suggests a pulmonary vasoconstrictor effect of AMP and DA/AMP. Adenine nucleotides have been implicated in the production of vasoconstrictor prostanoids (19); however, in vitro, adenosine causes a dose-dependent vasodilation of small pulmonary arteries (20). As expected SNP and SNP/DA decreased pulmonary vascular resistance.

The effects of AMP are likely to have been mediated by adenosine receptor stimulation because AMP is rapidly dephosphorylated to adenosine by 5′-

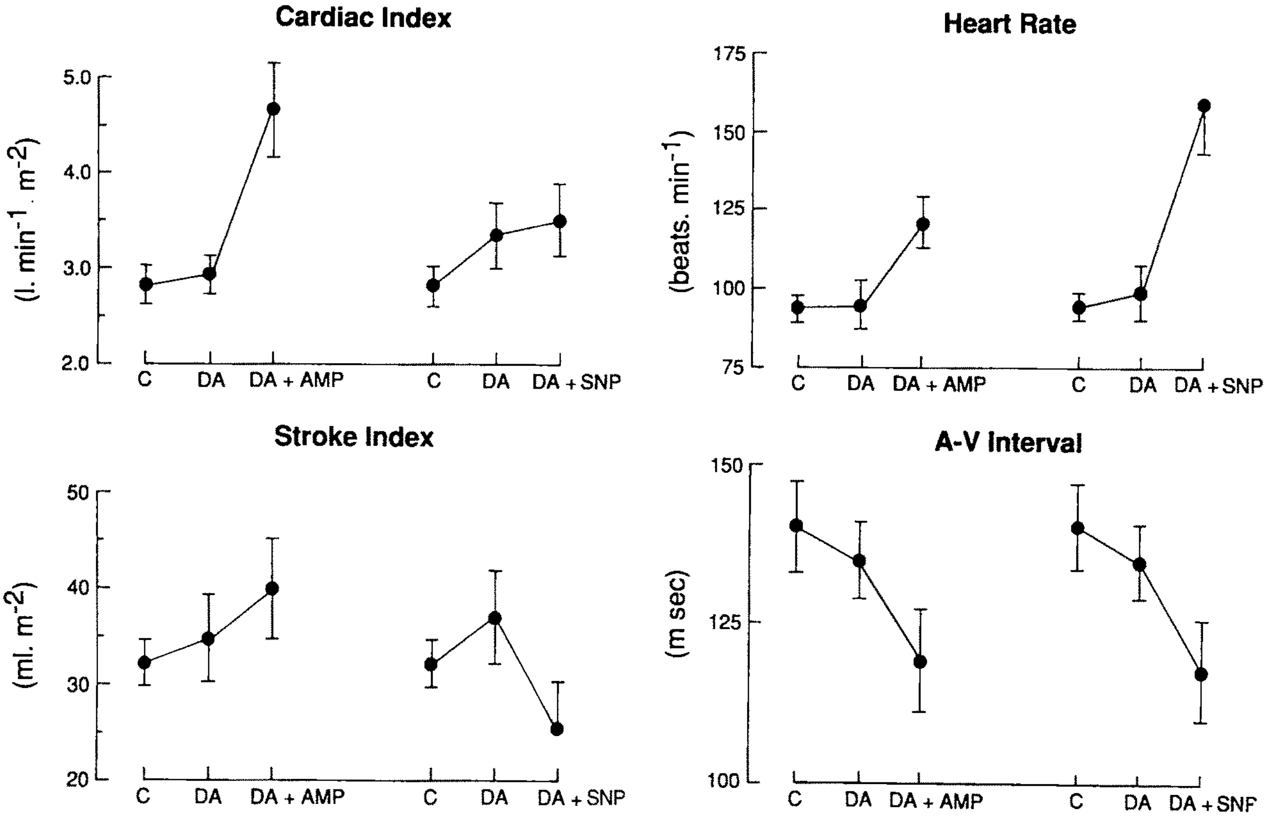


Figure 6. Effects of reducing MAP to 80 mm Hg by AMP or SNP during DA infusion (5 $\mu g \cdot kg^{-1} \cdot min^{-1}$) on cardiac index, stroke index, heart rate, and AV nodal conduction interval of anesthetized dogs. Values are given for baseline (C), DA alone (DA), and combinations of DA with AMP (DA + AMP) or DA with SNP (DA + SNP). Points represent the mean ± SEM ($n = 8$).

nucleotidase located on the plasma membrane of many cells, including vascular endothelial cells (21). Nevertheless, it is not clear if all AMP-induced responses were due to adenosine formation. Adenosine monophosphate is three to four times less potent on a molar basis than adenosine as a coronary vasodilator (22) and although the adenosine receptor antagonist 8-phenyltheophylline significantly antagonizes adenosine-induced vascular relaxation, responses to ATP are unchanged (23). These observations suggest that differences exist in the mechanisms of the vasoactivity of adenosine and its nucleotides. Adenosine monophosphate was used in this study because its greater aqueous solubility allowed effective plasma concentrations to be achieved without significant fluid loading.

An advantage of AMP over SNP observed in these experiments includes the stability of the hypotensive response during continuous intravenous infusion. As noted previously (10), SNP-induced vasodilation is associated with tachyphylaxis, probably by activation of the renin-angiotensin system and enhanced sympathetic activity. In contrast, renin (8) and norepinephrine (24) release is inhibited by adenosine receptor activation. This may explain the stable and therefore controllable vasodilator effect that was obtained by AMP infusions.

A major potential adverse effect of adenosine receptor agonists is their detrimental effect on renal perfusion. Our results demonstrate that AMP induced a transient (30 s) decrease in renal artery blood flow after which total flow returned to normal during continuous infusion. In addition, no antagonism by AMP of DA-induced renal vasodilation was observed. Injection of adenosine into the renal artery causes a more profound but qualitatively similar biphasic effect (25) with a return to normal blood flow on continuous infusion. However, maldistribution of blood flow within the kidney persists with low cortical and high medullary blood flows (26). The effects of systemic administration of AMP, and in particular its interaction with DA on the distribution of renal blood flow, deserve further study. Adenosine dilates coronary arterioles and in animal models of acute single vessel occlusion, adenosine can induce coronary steal (27,28). This suggests that adenosine would need to be used with caution in the 20% of subjects whose coronary anatomy is "steal-prone"

(29). Regional myocardial blood flow both in the normal and poststenotic collateral-dependent state should be evaluated during DA/AMP combinations. Information on the effects of adenosine infusion in conscious humans is limited. Infusion of low doses (70 $\mu g \cdot kg^{-1} \cdot min^{-1}$) increases effective pulmonary blood flow and decreases systemic vascular resistance without significantly altering heart rate or small airway resistance (30). Higher doses (100–200 $\mu g \cdot kg^{-1} \cdot min^{-1}$) are associated with increases in heart rate, minute ventilation, and subjective symptoms (headache, jaw pain, and chest discomfort) with no change in blood pressure (31). These symptoms may limit the utility of adenosine in conscious subjects but also may be attenuated or abolished by use of more selective adenosine receptor agonists.

The results of this study suggest that AMP offers significant advantages over SNP in situations where elevation of cardiac output and reduction in afterload are required. The combination of DA/AMP is also more effective than DA/SNP in this role.

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Hepatic Circulation and Oxygen Supply-Uptake Relationships After Hepatic Ischemic Insult During Anesthesia with Volatile Anesthetics and Fentanyl in Miniature Pigs

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Edwin L. Bradley, Jr, PhD

NAGANO K, GELMAN S, PARKS D, BRADLEY BL, Jr. Hepatic circulation and oxygen supply-uptake relationships after hepatic ischemic insult during anesthesia with volatile anesthetics and fentanyl in miniature pigs. Anesth Analg 1990;70:53–62.

The objective of the present study was to quantitate the effects of several anesthetics on hepatic circulation, oxygenation, and function after hepatic ischemic insult and during reperfusion. We examined the effects of different anesthetics on hepatic circulation, oxygenation, and function after hepatic ischemic insult in 28 miniature pigs weighing 20–27 kg. The preparation allowed a stepwise decrease followed by a complete cessation for 1 h of hepatic blood and oxygen supply. Immediately after the unclamping of both vessels supplying the liver and restoration of the hepatic circulation, systemic mean arterial pressure decreased to ~75% of preischemic values in animals anesthetized with pentobarbital and fentanyl and to 60% of preischemic values in pigs anesthetized with halothane, enflurane, or isoflurane. Total hepatic blood flow immediately returned to preischemic values without significant difference between the groups. Subsequently, hepatic oxygen delivery returned to 75%–95% of preischemic values. Hepatic oxygen uptake returned to 50%–60% of preischemic values in animals anesthetized with pentobarbital and with volatile anesthetics and up to 80% and then later to baseline values with fentanyl anesthesia. Lactate uptake by the liver returned to preischemic values only in animals given fentanyl or isoflurane but remained at ~50% of preischemic values during enflurane and 20%–40% during halothane and pentobarbital anesthesia. Thus, the study indicates that both isoflurane and fentanyl anesthesia provide more protection from ischemic insult than do halothane, enflurane, or pentobarbital anesthesia.

Key Words: LIVER, BLOOD FLOW. ANESTHETICS, VOLATILE—halothane, enflurane, isoflurane. ANESTHETICS, INTRAVENOUS—fentanyl.

Temporary interruption of hepatic blood supply is needed during many surgical procedures involving the thoracic aorta, hepatic trauma, and, of course, liver transplantation. The effects of temporary ischemia on liver function have recently attracted much attention, including the effects of reperfusion on different hepatic cellular functions (1–4). Other important aspects of viability, namely, hepatic circulation and oxygen supply after ischemia and reperfusion, have attracted much less attention. There are some data suggesting that ischemia/reperfusion-induced microcirculatory disturbances, resulting in a decrease in tissue perfusion and often called the "no reflow" phenomenon, which is often observed in the heart (5), may also occur in the liver after an ischemic insult (2,4,6).

It is well known that some anesthetics may protect certain tissues from ischemic insults better than others. For example, barbiturates and isoflurane, unlike other anesthetics, can protect the brain from an ischemic insult by decreasing cerebral oxygen demand (7). Isoflurane can enhance metabolic recovery of the myocardium during the postischemic period (8).

Anesthetics affect hepatic oxygen supply/demand in various ways and to different degrees. For example, halothane decreases hepatic blood flow and

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oxygen supply to a much greater extent than does isoflurane (9,10), thereby predisposing the liver to hypoxic injury. In contrast, halothane decreases hepatic oxygen demand while isoflurane apparently does not (11). Thus, there are sufficient data in the literature to hypothesize that different anesthetics can alter, in various ways, hepatic circulation, oxygenation, and function during and after hepatic ischemia.

There are no substantiated recommendations and no information in the literature regarding the effects of different anesthetics administered before and during hepatic ischemia on hepatic function and circulation during reperfusion. Information in this area is clinically important. The main hypothesis of this study can be formulated as follows: anesthetics have different effects on hepatic circulation and function during ischemia and reperfusion and thus may provide different degrees of protection of the liver associated with impaired hepatic circulation. The objective of the present study was to quantitate the effects of several commonly used anesthetics on hepatic circulation, oxygenation, and function after hepatic ischemic insult and during reperfusion.

Methods

Anesthesia

The study was approved by the Institutional Animal Use Committee. Twenty-eight female miniature pigs, weighing 20–27 kg, fasted for 24 h. Anesthesia induction was achieved with sodium methohexital, 20 mg/kg IM. Muscle relaxation was achieved with pancuronium bromide, 0.1 mg/kg. Controlled ventilation with nitrous oxide (60%) in oxygen to maintain a $Paco_2$ of 35–40 mm Hg was provided through an endotracheal tube using an Air-Shield ventilator. Body temperature was monitored rectally and maintained with a heating pad at 38°C. Throughout the experiments, Ringer's solution was infused at a rate of 5 $mL \cdot kg^{-1} \cdot h^{-1}$.

After anesthesia induction and before surgical preparation, the animals were divided into five groups: six animals were anesthetized with halothane at 0.9% end-expired concentration (group H), five animals were anesthetized with isoflurane at 1.5% end-expired concentration (group I), six animals were anesthetized with enflurane at 2.2% end-expired concentration (group E), six animals were anesthetized with fentanyl (group F), and the remaining five animals were anesthetized with sodium pentobarbital (group P). At the end of surgical preparation, nitrous oxide was discontinued while end-expired concentrations of volatile anesthetics were unchanged throughout the experiments, regardless of changes in systemic hemodynamics. The end-expired concentrations of volatile anesthetics were determined with a Puritan-Bennett Corp. (Overland Park, Kan.) Datex anesthetic agent monitor model AM222.

Group F animals received fentanyl is a dose of 100 $\mu g/kg$ followed by a constant infusion of 50 $\mu g \cdot kg^{-1} \cdot h^{-1}$. The arterial concentrations of plasma fentanyl were measured before ischemic insult, after hepatic ischemia before reperfusion, and at the 15th minute of reperfusion, using radioimmunoassay (12).

Sodium pentobarbital was administered in a dose of 30 mg/kg IV followed by infusion at a rate of 1–2 $mg \cdot kg^{-1} \cdot h^{-1}$ in group P animals.

Surgical Preparation

Surgical preparation included isolation of both carotid arteries and jugular veins, one carotid artery being cannulated for recording of blood pressure and blood sampling, the other being used for blood supply to the hepatic artery (see below). The left jugular vein was cannulated for fluid infusion and drug administration. Laparotomy was performed; heparin in a dose of 300 U/kg was administered intravenously. Portal vein was isolated and transected. A tubing of appropriate size, supplied with a cannulating electromagnetic flowmeter probe for measurements of portal blood flow and a port for measuring portal venous pressure, was inserted into the portal vein so that the portal blood would flow through the proximal end of the transected portal vein, the tubing with the probe and the port for flow and pressure measurements, and the distal (hepatic) end of the portal vein. In addition, this tubing was supplied with a Y-connector that linked the tubing with the left jugular vein. The preparation allowed interruption of the portal blood flow to the liver without interrupting the outflow from the preportal area by redirecting portal blood flow into the jugular vein in the following way. The inserted tubing could be gradually constricted between the electromagnetic flowmeter probe and the hepatic end of the portal vein; simultaneously the linkage of the tubing with the jugular vein could be opened, redirecting portal blood flow into the jugular vein and thereby preventing the congestion of preportal organs and tissues (Figure 1).

All visible small branches of the hepatic artery as well as the left gastric artery and the gastroduodenal artery were ligated. The hepatic artery was then transected. The proximal end of the hepatic artery

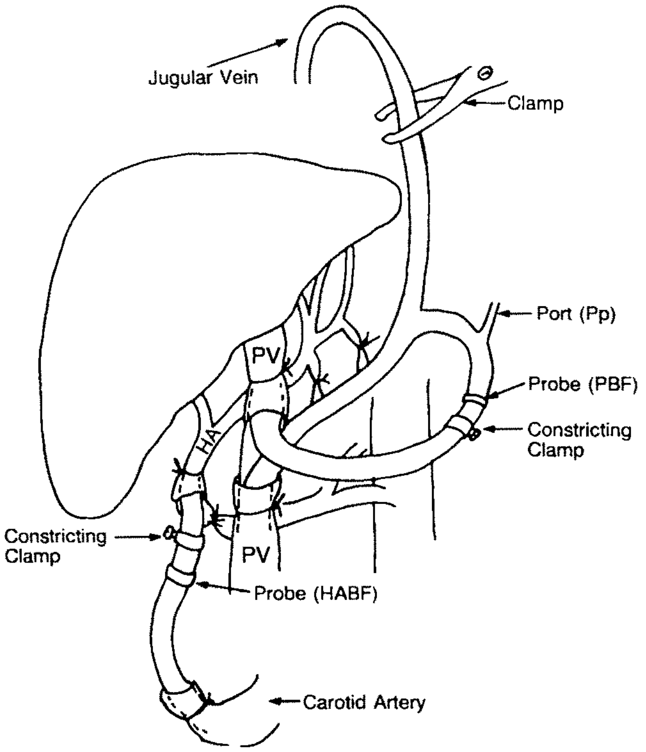

Figure 1. Schematic representation of the experimental preparation. Abbreviations: HA, hepatic artery; PV, portal vein; Port (Pp), port in the tubing connecting two ends of transected portal vein for portal pressure (P_p) measurements; probe (PBF), electromagnetic flowmeter probe inserted into the tubing connecting both ends of transected portal vein for portal blood flow (PBF) measurements; probe (HABF), electromagnetic flowmeter probe inserted into the tubing connecting carotid and hepatic end of the hepatic artery for hepatic arterial blood flow (HABF) measurements. See text for detailed explanation.

was ligated. The previously exposed carotid artery and distal (hepatic) end of the hepatic artery were connected one with the other with a tubing of appropriate size supplied with an electromagnetic flowmeter probe of appropriate size. A constricting clamp was placed on the tubing between the electromagnetic flowmeter probe and the hepatic end of the hepatic artery, which allowed decrease and interruption of arterial blood supply to the liver.

The hepatic vein in the median lobe was cannulated subdiaphragmatically through the inferior (posterior) caval vein with a balloon-tipped catheter for pressure monitoring and blood sampling. The catheter was advanced into the hepatic vein up to wage position, and then withdrawn 3 cm to ensure free positioning of the catheter tip in the hepatic vein. The balloon was slightly inflated and blood samples were slowly withdrawn making sure that blood from the caval vein did not mingle with the hepatic venous blood. The position of this catheter was verified after each experiment.

Experimental Protocol

Thirty minutes after completion of the preparation, baseline measurements were made and blood samples obtained. The hepatic artery was then occluded and portal blood flow was gradually decreased to zero within 60 min by stepwise constricting of the tubing connecting the transected ends of the portal vein. To prevent venous congestion, the blood draining the preportal tissues was redirected through the Y-connector into the jugular vein. After 60 min of total hepatic ischemia, both vessels—hepatic artery and portal vein—were simultaneously unclamped while flow from the preportal area to the jugular vein was stopped. All measurements were repeated, and blood samples were obtained 30, 60, and 90 min after starting reperfusion. Five animals (two in the pentobarbital group and one in each group of animals receiving a volatile anesthetic) died during the first 10 min of reperfusion. No efforts to resuscitate the animals were made. Only the remaining 28 animals who survived 90 min of reperfusion are included in the analysis of the study.

Measurements and Calculations

Measurements included systolic, diastolic, and mean systemic arterial (MAP) pressures, and portal venous and hepatic venous pressures. Arterial, portal, and hepatic venous blood samples were obtained for measurements of pH/gas tensions and oxygen content using an Instrumentation Laboratory, Inc. (Lexington, Mass.) model 1301 pH/blood gas analyzer and model 282 Co-oximeter. Whole-blood lactate concentrations were determined spectrophotometrically in arterial, portal, and hepatic venous blood samples using a modification of the method of Marbach and Weil (13), which employed the oxidation of lactate to pyruvate. The enzymatic method selected for the analysis has greater specificity than chemical oxidation procedures. Samples were treated with 6% perchloric acid.

Additional samples from arterial blood were taken for measurements of lactate dehydrogenase (LDH) using a method modified from Wacker et al. (14), which catalyzes the conversion of L-lactate to pyruvate in the presence of nicotinamide adenine dinucleotide (NAD^+). The enzymatic activity of LDH is proportional to the rate of production of reduced nicotinamide adenine dinucleotide (NADH). The amount of NADH produced was determined by measuring the increase of absorptance at 340 nm.

Glutamic pyruvic transaminase-alanine aminotransferase (GPT) was measured by a method modified from Henry et al. (15) that employs catalysis of the transamination from L-alanine to α-ketoglutamate, forming L-glutamate and pyruvate. The pyruvate formed is reduced to lactate by LDH with simultaneous oxidation of NADH.

Glutamic oxaloacetic transaminase-asparate aminotransferase (GOT) was measured using a method described by Kato et al. (16).

Alcohol dehydrogenase (ADH) activity was measured by the method of Kato et al. (16,17). Briefly, ethanol is oxidized to acetaldehyde by ADH, and NAD^+ is proportionally reduced to NADH; therefore, ADH activities can be measured by the change in absorptance at 340 nm. Alcohol dehydrogenase is a relatively liver-specific enzyme that is localized in the cytoplasm of hepatocytes especially in the centrilobular region of the liver lobule (18). Therefore, it may be a suitable marker for ischemic liver injury, which is often accompanied by hepatic centrilobular necrosis (17). Alcohol dehydrogenase activities in the serum of arterial blood were <1 U/L before surgical preparation.

All enzymes were measured by a Gilford Instrument Laboratories (Oberlin, Ohio) UV-VIS spectrophotometer. Absorptance data were converted into the reportable enzyme activity values (units per liter of serum) based on calculations for zero-order kinetics.

Hepatic oxygen delivery (HDo_2) was calculated as the sum of the product of multiplication of hepatic arterial blood flow and arterial oxygen content ($HABF \times C_ao_2$) and the product of portal blood flow times oxygen content in portal blood ($PBF \times C_{pv}o_2$). Hepatic oxygen uptake ($H\dot{V}o_2$) was calculated as a difference between HDo_2 and the product of total hepatic blood flow (THBF = sum of HABF and PBF) times oxygen content of hepatic venous blood ($C_{hv}o_2$). Hepatic oxygen supply-uptake gradients and ratios, and hepatic oxygen extraction ($H\dot{V}o_2/HDo_2 \times 100$) were also calculated. Total splanchnic vascular (SPVR), hepatic arterial (HAR), portal venous (PVR), and preportal vascular (PPVR) resistances (expressed in $mm\ Hg \cdot mL^{-1} \cdot min \cdot g$) were calculated as follows:

$$SPVR = \frac{MAP - HVP}{THBF},$$

$$HAR = \frac{MAP - HVP}{HABF},$$

$$PVR = \frac{PVP - HVP}{PBF},$$

$$PPVR = \frac{MAP - PVP}{PBF},$$

where PBF, HABF, and THBF are portal venous, hepatic arterial, and total hepatic blood flows, respectively in $mL \cdot min^{-1} \cdot 100\ g^{-1}$. MAP, HVP, and PVP are mean arterial, hepatic venous, and portal venous pressures, respectively in mm Hg.

Lactate uptake by the liver was calculated as follows:

$$L_u = (C_aL \times HABF + C_{pv}L \times PBF) - C_{hv}L \times (HABF + PBF),$$

where L_u = lactate uptake by the liver in $mg \cdot min^{-1} \cdot 100\ g^{-1}$; $C_{hv}L$, C_aL, and $C_{pv}L$ = lactate concentrations in hepatic venous, arterial, and portal venous blood, respectively in $mg \cdot min^{-1} \cdot 100\ g^{-1}$; HABF and PBF = hepatic arterial and portal blood flows in $mL \cdot min^{-1} \cdot 100\ g^{-1}$, respectively.

Hemodynamic and blood gas data were analyzed as both absolute values and percentage of baseline values. The data were summarized as the mean ± SEM for each group and stage unless specified otherwise. Comparisons among groups at each stage utilized a one-way analysis of variance. Individual comparisons of a pair of means used Fisher's protected least significance difference test. Comparisons among stages for each group were made by a repeated measures analysis of variance (19).

Results

The baseline values of the variables characterizing hepatic circulation and hepatic oxygen supply-uptake relationships observed before hepatic ischemic insult are presented in Tables 1 and 2, respectively. The concentrations of fentanyl in arterial blood (mean ± SD) were 30.1 ± 9.9 ng/mL at stage 1, before ischemic insult to the liver, 45 ± 11.6 ng/mL at the end of the ischemic period, and 45.6 ± 12.4 ng/mL 15 min after reperfusion. Immediately after unclamping of both vessels supplying the liver and restoration of the hepatic circulation, systemic MAP decreased to ~75% of the preischemic values in animals anesthetized with pentobarbital or fentanyl and to ~60% of the preischemic values in pigs anesthetized with volatile anesthetics, without significant difference among halothane, enflurane, and isoflurane groups (Figure 2). Total hepatic blood flow was immediately restored to preischemic values without significant differences among the groups (Figure 3). Portal blood flow was also restored toward preischemic values without differences among the groups, but values of flow were 25%–40% below the preischemic values in animals anesthetized with fentanyl and pentobarbital (Figure 4). Hepatic arterial blood flow increased rather

Table 1. Variables Characterizing Hepatic Circulation Before Hepatic Ischemia

Variable	Halothane	Isoflurane	Enflurane	Fentanyl	Pentobarbital
MAP (mm Hg)	100 ± 10	112 ± 17	111 ± 18	$139 \pm 12^{a,b,c}$	126 ± 4
HABF ($mL \cdot min^{-1} \cdot 100\ g^{-1}$)	16 ± 7	23 ± 4	18 ± 13	17 ± 13	18 ± 8
PBF ($mL \cdot min^{-1} \cdot 100\ g^{-1}$)	49 ± 9^{b}	$84 \pm 14^{a,c,d}$	64 ± 17^{b}	$80 \pm 8^{a,c,d}$	65 ± 13^{b}
THBF ($mL \cdot min^{-1} \cdot 100\ g^{-1}$)	65 ± 14^{b}	$108 \pm 12^{a,c,d}$	82 ± 25^{b}	$97 \pm 13^{a,c,d}$	83 ± 19^{b}
HAVR ($mm\ Hg \cdot mL^{-1} \cdot min \cdot g$)	714 ± 355	461 ± 108	709 ± 252	857 ± 518	30 ± 258
PPVR ($mm\ Hg \cdot mL^{-1} \cdot min \cdot g$)	181 ± 34^{b}	$122 \pm 31^{a,c,d}$	160 ± 24^{b}	158 ± 17	180 ± 36^{b}
PVR ($mm\ Hg \cdot mL^{-1} \cdot min \cdot g$)	10.6 ± 5.0	5.1 ± 1.7^{d}	6.5 ± 2.7	6.7 ± 2.6	8.8 ± 7.2^{b}
SPVR ($mm\ Hg \cdot mL^{-1} \cdot min \cdot g$)	148 ± 32^{b}	$99 \pm 23^{a,c,d}$	132 ± 26^{b}	137 ± 23	150 ± 35^{b}

MAP, mean arterial pressure; HABF, PBF, THBF, hepatic arterial, portal, and total hepatic blood flows, respectively; HAVR, PPVR, PVR, SPVR, arterial, preportal, portal, and total splanchnic vascular resistances, respectively.

Values given as mean ± SD.

[a] $P < 0.05$ vs halothane.

[b] $P < 0.05$ vs isoflurane.

[c] $P < 0.05$ vs enflurane.

[d] $P < 0.05$ vs pentobarbital.

Table 2. Variables Characterizing Hepatic Oxygen Supply-Uptake Relationship Before Hepatic Ischemia

Variable	Halothane	Isoflurane	Enflurane	Fentanyl	Pentobarbital
HDo_2 ($mL \cdot min^{-1} \cdot 100\ g^{-1}$)	8.6 ± 2.1^{a}	$14.4 \pm 0.8^{b,c}$	11.4 ± 3.3^{a}	$14.0 \pm 3.5^{b,c,d}$	11.1 ± 2.8^{a}
$H\dot{V}o_2$ ($mL \cdot min^{-1} \cdot 100\ g^{-1}$)	$3.4 \pm 0.4^{a,c,d}$	5.0 ± 1.0^{b}	5.9 ± 0.9^{b}	4.9 ± 1.4^{b}	5.1 ± 1.0^{b}
L_u ($mg \cdot min^{-1} \cdot 100\ g^{-1}$)	4.9 ± 1.7	5.9 ± 3.2	6.0 ± 2.0	6.2 ± 4.4	4.8 ± 1.9
L_a (mg/dL)	16.3 ± 3.0	14.8 ± 4.3	15.5 ± 4.5	13.0 ± 8.1	17.4 ± 6.2
LDH (U/L)	271 ± 57	240 ± 40	260 ± 68	$393 \pm 133^{a,b,c}$	304 ± 53
GPT (U/L)	18 ± 3	17 ± 3	17 ± 6	$21 \pm 3^{b,c}$	20 ± 4
GOT (U/L)	58 ± 18	55 ± 17	54 ± 12	$78 \pm 21^{a,b,c}$	64 ± 18
ADH (U/L)	0.6 ± 0.4	0.5 ± 0.6	0.4 ± 0.3	0.5 ± 0.5	0.4 ± 0.4

HDo_2 and $H\dot{V}o_2$, hepatic oxygen delivery and hepatic oxygen uptake; L_u, lactate uptake by the liver; L_a, lactate concentration in arterial blood; LDH, GPT, GOT, ADH, concentrations of lactate dehydrogenase, glutamic pyruvic transaminase-alanine aminotransferase, glutamic-oxaloacetic transaminase-aspartate aminotransferase, and alcohol dehydrogenase, respectively.

Values given as mean ± SD.

[a] $P < 0.05$ vs isoflurane.

[b] $P < 0.05$ vs halothane.

[c] $P < 0.05$ vs enflurane.

[d] $P < 0.05$ vs pentobarbital.

substantially upon reperfusion compared with preischemic values: the values on reperfusion were practically doubled in animals given fentanyl or pentobarbital whereas the values of hepatic arterial blood flow in pigs anesthetized with halothane or isoflurane did not exceed the values observed before ischemic insult (Figure 5). Total splanchnic vascular resistance, therefore, returned to approximately preischemic levels in animals anesthetized with pentobarbital, isoflurane, or fentanyl and were at ~50% of preischemic values in animals anesthetized with enflurane and halothane. Portal venular resistance exceeded preischemic values by 30%–60% without significant differences among the groups. Hepatic arterial vascular resistances were below preischemic values with all five anesthetics studied. Preportal venular resistances returned to preischemic values immediately upon reperfusion in animals treated with pentobarbital, isoflurane, or fentanyl, and were 50%–70% below preischemic values in animals anesthetized with enflurane or halothane.

Oxygen content and saturation in hepatic venous blood during reperfusion exceeded preischemic levels in animals anesthetized with enflurane and reached preischemic values in hepatic venous blood in the four remaining groups without significant difference among the groups or from preischemia.

Hepatic oxygen delivery returned to 75%–95% of preischemic values after 30 min of reperfusion. There was a tendency for hepatic oxygen delivery to decrease during the following hour of observation. There were no statistically significant differences in hepatic oxygen delivery among the groups (Figure 6). Hepatic oxygen uptake returned to 50%–60% of preischemic values in animals anesthetized with volatile anesthetics and pentobarbital. There was not a clear tendency for hepatic oxygen uptake to change during the period of observation in these groups. On the other hand, hepatic oxygen uptake in animals given fentanyl returned to 80% of preischemic values after 30 min of reperfusion and was restored completely by the end of the experiment (90 min of reperfusion)

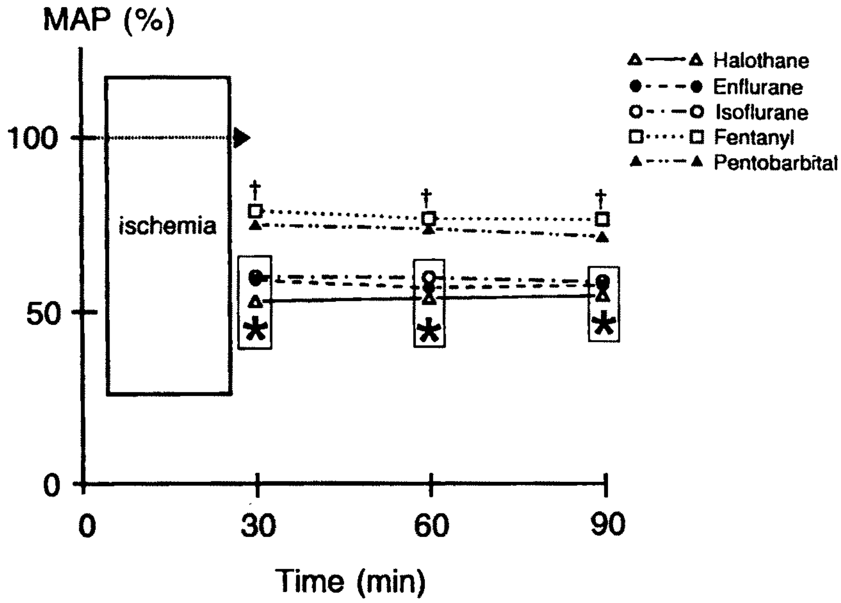

Figure 2. Changes in mean arterial pressure (MAP) during reperfusion expressed as a percentage of preischemic values. *30, 60, 90* signify minutes after unclamping of the hepatic artery and portal vein. ✱ = $P < 0.05$ vs preischemic values for the groups included in the square; † = $P < 0.05$ vs halothane at corresponding stage.

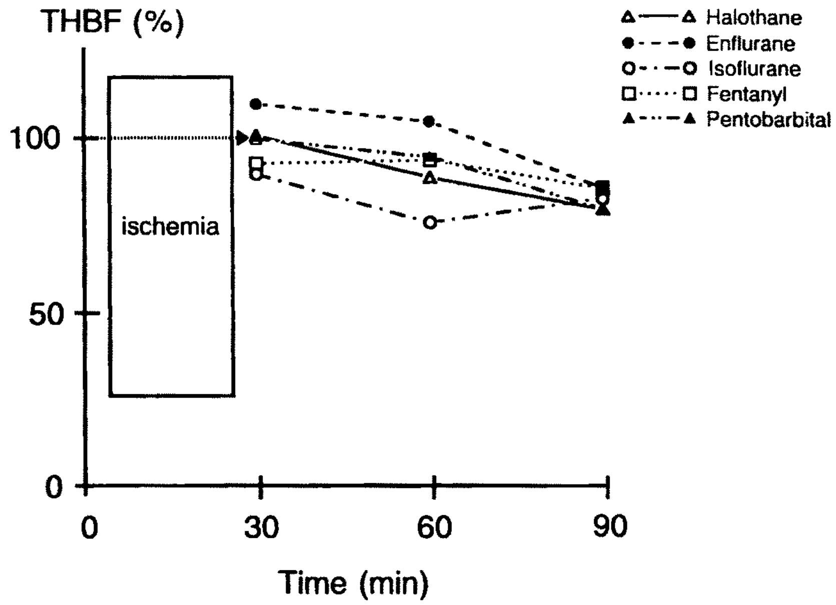

Figure 3. Changes in total hepatic blood flow (THBF) during reperfusion expressed as a percentage of preischemic values. For symbols' identification see legend to Figure 2.

(Figure 7). Oxygen extraction ratio was decreased at 30 min of reperfusion in all groups except fentanyl, where it was unchanged. At 60 and 90 min of reperfusion, however, the ratio returned to baseline values in all groups without significant difference among them.

Concentrations of the measured enzymes (LDH, GPT, GOT, ADH) in arterial blood increased rather substantially (7–24-fold) without significant differences among the groups. There was a significant continuous increase in all enzyme concentrations with time, during the 30–90 min of observation after hepatic perfusion was reestablished (data not shown). Liver function, as evaluated by changes in lactate uptake by the liver, returned to preischemic values in the isoflurane and fentanyl groups within 60 and 90 min of reperfusion, respectively (Figure 8). Lactate uptake by the liver was ~50% of preischemic values in the enflurane and 20%–40% in the halothane and pentobarbital groups, without significant differences among these three groups and without an obvious tendency to change during the period of reperfusion (Figure 8).

Discussion

The model used in this study allowed production of hepatic ischemia in vivo without congestion or isch-

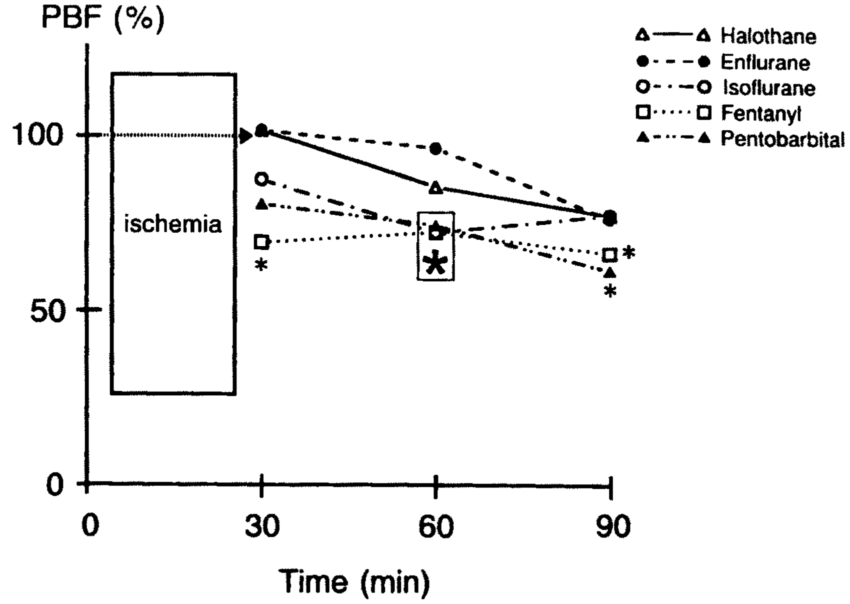

Figure 4. Changes in portal blood flow (PBF) during reperfusion expressed as a percentage of preischemic values. For symbols' identification see legend to Figure 2. *$P < 0.05$ vs preischemic values. ✱ = $P < 0.05$ vs preischemic values for the groups included in the square.

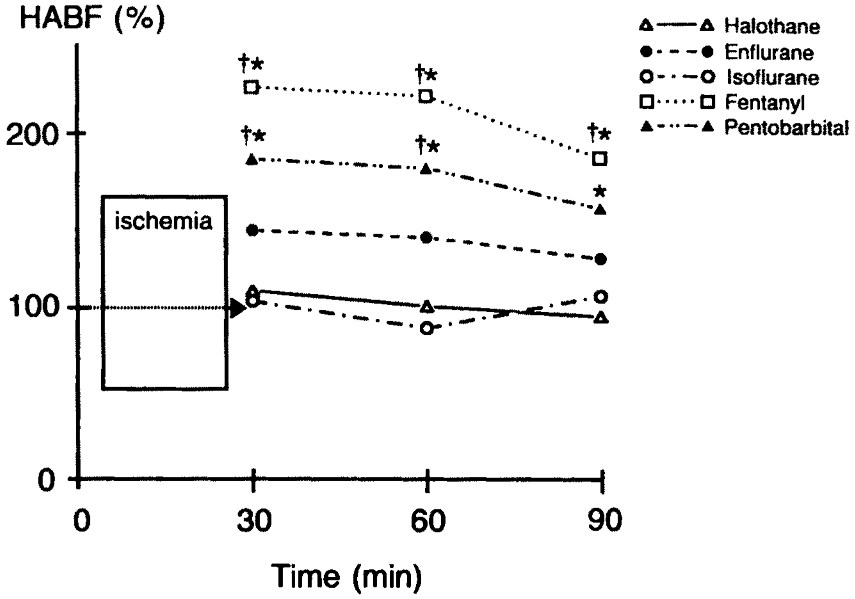

Figure 5. Changes in hepatic arterial blood flow (HABF) during reperfusion expressed as a percentage of preischemic values. For symbols' identification see legend to Figures 2 and 4.

emia in the preportal tissues. This model also allowed examination of responses upon restoration of hepatic circulation after ischemic insult. The four drugs widely used in modern anesthesia, as well as pentobarbital as a control, were examined under similar conditions. The main limitation of the study is that only one concentration/dose of each anesthetic and one incidence of ischemia were studied. However, the main thrust of this study was to provide a type of anesthetic management as close to a clinical situation as possible, and to determine which anesthetic in clinically relevant situations could provide the most effective restoration of hepatic function after oxygen deprivation. The fact that the depth of anesthesia provided during the experiments was associated with relatively similar values of mean arterial pressure in animals anesthetized with volatile anesthetics (Table 1) reinforces the clinical relevance of these experiments. Another limitation of the study is related to an absence of nonanesthetized group: hepatic ischemia and reperfusion without anesthesia. For obvious ethical reasons, a study with prolonged hepatic ischemia could not be performed on a conscious animal. Finally, the effects of residual methohexital concentrations on the overall results cannot be ruled out. However, the relatively short half-life of methohexital

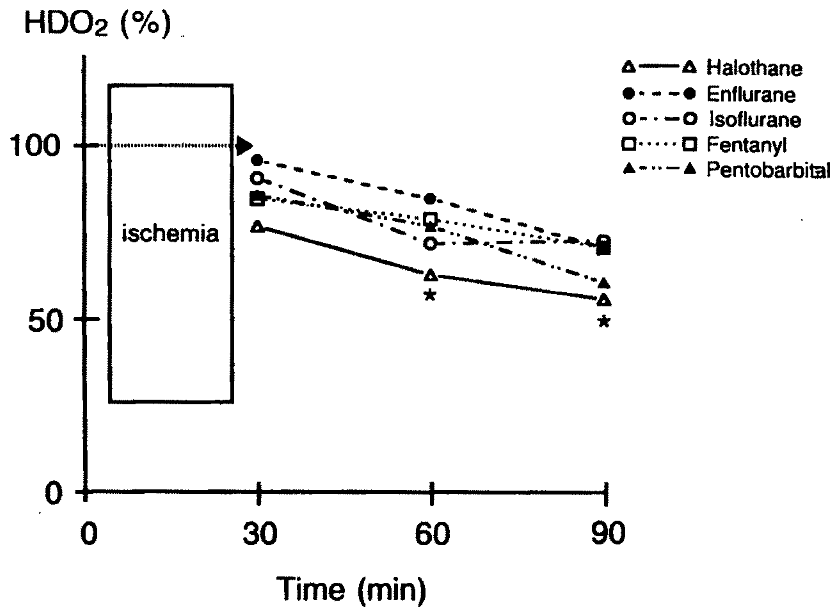

Figure 6. Changes in hepatic oxygen delivery (HDo_2) during reperfusion expressed as a percentage of preischemic values. For symbols' identification see legend to Figures 2 and 4.

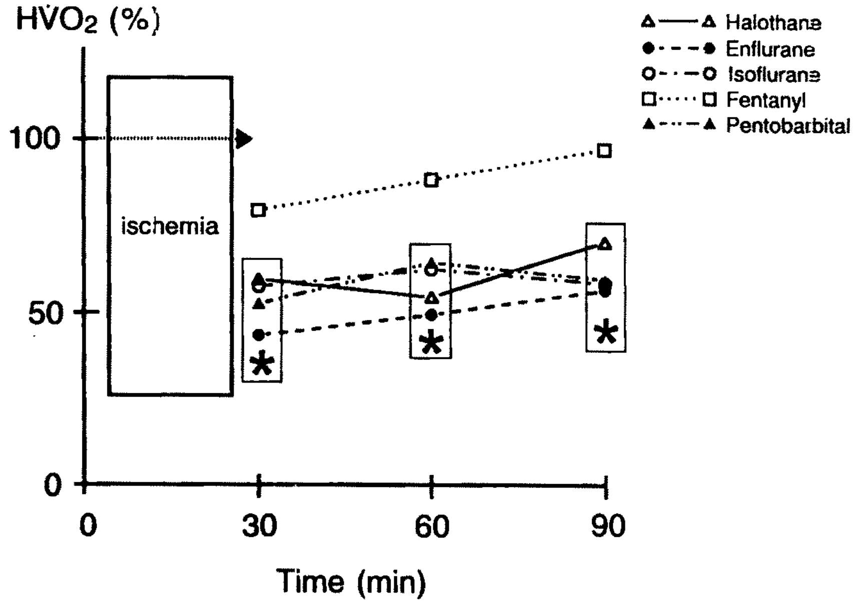

Figure 7. Changes in hepatic oxygen uptake (HVo_2) during reperfusion expressed as a percentage of preischemic values. For symbols' identification see legend to Figure 2.

(20) and the observed differences among the experimental groups suggest that the role of methohexital in these experiments was negligible.

During reperfusion after hepatic ischemia, systemic arterial hypotension was observed (Figure 2). Probably this hypotension is related to vasoactive, primarily vasodilating substances, washed out from the reperfused ischemic liver. This systemic arterial hypotension, however, was associated with decreases in vascular resistances in the hepatic vasculature and a virtually complete restoration of total hepatic blood flow (Figure 3). It is worth noting that vascular resistance decreased more in the hepatic arterial vasculature than in preportal vascular bed. Accordingly, the values of hepatic arterial blood flow during reperfusion were greater than or equal to preischemic values (Figure 5). The observed decrease in portal blood flow during reperfusion could be due to cell swelling which may have resulted from an ischemia-mediated loss of the ability of hepatic cells to maintain normal water and electrolyte balance (21). Such swelling does indeed occur after hepatic ischemia and reperfusion (6,22) and, by reducing the diameter of the vascular lumen, impedes blood flow through the portal venous vasculature. However, values of hepatic arterial blood flow were equal to (in halothane and isoflurane groups) or greater than (in animals treated with other anesthetics) those ob-

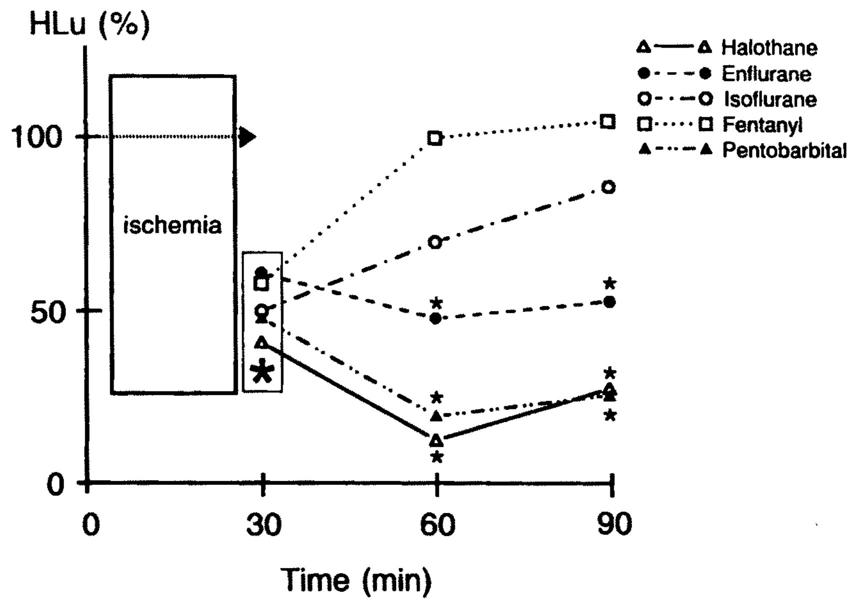

Figure 8. Changes in hepatic lactate uptake (HL_u) during reperfusion expressed as a percentage of preischemic values. For symbols' identification see legend to Figures 2 and 4.

served before ischemic insult (Figure 5). These observations might suggest that the "no reflow" phenomenon (2,4) develops earlier in the portal than in the hepatic arterial microvasculature. It is important to realize that an increase in hepatic arterial blood flow on reperfusion was observed despite a rather substantial decrease in systemic arterial blood pressure. These observations may reflect the fact that after ischemic insult, hepatic arterial vasculature was still able to respond reciprocally to a decreased portal blood flow. In a normal liver, the relationship between hepatic arterial and portal blood flows is reciprocal and, accordingly, any decrease in portal blood flow is associated with compensatory increases in hepatic arterial blood flow (22,23).

Hepatic oxygen delivery did not return to preischemic values during reperfusion (Figure 6), but it was adequate as the values of oxygen content and saturation in hepatic venous blood returned to control values and oxygen extraction did not increase. Therefore, the lack of restoration of hepatic oxygen uptake to preischemic values in animals treated with every examined anesthetic except fentanyl (Figure 7) suggests that the decrease in hepatic oxygen uptake is mainly due to a decrease in the ability of the hepatic cells (or to a decrease in the number of nondamaged viable hepatic cells) to consume oxygen and restore function. The data regarding changes in lactate uptake by the liver (Figure 8) indirectly support this notion; in spite of an adequate restoration of hepatic blood flow and hepatic oxygen supply, lactate uptake by the liver, which reflects hepatic function, did not return to control values in animals anesthetized with enflurane, halothane, or pentobarbital. However, lactate uptake was restored relatively rapidly after reperfusion in animals treated with isoflurane and somewhat later in animals treated with fentanyl (Figure 8). Substantial increases in enzyme concentrations without differences among the groups suggest that enzyme release from the liver is a sensitive marker of hepatic damage and that the ischemic insult was too severe to be modified by the anesthetics. The values of hepatic oxygen uptake in conditions of adequate hepatic oxygen delivery, and particularly the values of lactate uptake by the liver, reflect the degree of preservation and/or restoration of the hepatic function after hepatic ischemic insult.

The present results demonstrate that hepatic vasculature function, particularly hepatic arterial vasculature function, returns rather quickly after an ischemic insult, and that the disturbances mediated by the ischemia at the cellular level play a more important role during postischemia and reperfusion than restoration of the hepatic blood and oxygen supply per se.

Thus, the posed hypothesis, namely that different anesthetics might provide different degrees of protection from hepatic ischemia is supported: liver function was restored more rapidly and to a somewhat greater extent in animals anesthetized with isoflurane or fentanyl than in animals anesthetized with halothane, enflurane, or pentobarbital. It is important to realize that the observed differences represent relatively acute changes and may not accurately reflect changes or differences on a more long-term basis. The possible clinical implications of the observed results are that during the anesthetic management of patients undergoing surgery requiring the temporary interruption of hepatic blood and oxygen supply, anesthetic management using isoflurane and/or fentanyl may be preferable to the use of halothane or enflurane.

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Immunoreactive Substance P Is Decreased in Saliva of Patients with Chronic Back Pain Syndromes

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PARRIS WCV, KAMBAM JR, NAUKAM RJ, RAMA SASTRY BV. Immunoreactive substance P is decreased in saliva of patients with chronic back pain syndromes. Anesth Analg 1990;70:63–7.

Substance P, a neuropeptide associated with pain perception, is widely distributed in the central nervous system and is decreased in the cerebrospinal fluid of chronic pain patients as compared with that of healthy human volunteers. In this study, we have demonstrated the presence of immunoreactive substance P in saliva and further, that both saliva and plasma levels of immunoreactive substance P are lower in patients with chronic low back pain than in healthy human volunteers. To our knowledge, this is the first time that substance P has been identified in human saliva. These findings, together with the noninvasive nature of saliva collection, suggest that substance P in saliva may be useful as an alternative neurochemical correlate of chronic low back pain when collection of cerebrospinal fluid and plasma samples for substance P analysis is unacceptable or inappropriate.

Key Words: POLYPEPTIDES, SUBSTANCE P.

Substance P, a member of the tachykinin family of neuropeptides, is present throughout the central nervous system with preferential distribution in the dorsal root of the spinal cord. Structurally it is an 11-amino acid polypeptide whose C-terminal amino acid sequence is essential for some of its pharmacologic activities (1). Cerebrospinal fluid (CSF) levels of substance P in patients with chronic pain have been shown to be lower than CSF levels of substance P in healthy human volunteers (2). As CSF collection is a relatively invasive (though safe) procedure (3), this study was undertaken to determine if other biological fluids might be used to detect differences in substance P between patients with chronic low back pain and healthy human volunteers. The clinical relevance of this study lies in the possible use of substance P in saliva as a neurochemical correlate of chronic low back pain when other methods are unacceptable or inappropriate.

Materials and Methods

Subjects

The study included nine patients with chronic low back pain syndrome who were being treated as outpatients at the Vanderbilt Pain Control Center. Four of the patients were women and five were men; the mean age was 46.7 yr. The duration of pain ranged from 10 mo to 8 yr with 37.7 mo being the average duration of the pain. All patients had chronic low back pain but none of the patients had previous back surgery. Two of the nine patients took no medication; the remaining patients took various nonsteroidal anti-inflammatory drugs, tranquilizers, and narcotic analgesics for pain control. The nine healthy human volunteers were physicians, nurses, and supporting staff at the Vanderbilt Pain Control Center. There were six women and three men and the mean age was 31.2 yr. All volunteers underwent the same procedures for blood and sputum collection as the chronic pain patients.

All patients were interviewed, examined, and managed by the medical staff of the Pain Control Center and were classified using the Emory Pain Classification Scale (4). All patients also completed the psychologic profile inventory: the Symptom Checklist-90 (5) (SCL-90). The SCL-90 consists of 90

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questions grouped into 10 subscales: somatization, obsessionality, paranoia, hostility, suicidal ideations, interpersonal sensitivity, phobia, anxiety, depression, and psychoticism. In addition to the present investigation, a plan of management was outlined for and explained to the patient.

After obtaining the approval of the Institutional Review Board and informed consent from each patient, 10 mL of peripheral venous blood was collected in ethylenediaminetetraacetate vacutainer tubes. Patients and volunteers were also asked to collect saliva in a sputum receptacle (kept on ice) using imagery as a stimulus to increase saliva production without direct pharmacologic intervention. The patients and volunteers were asked to reflect on chewing a bitter lemon and this produced adequate quantities of saliva in all cases. Usually, about 2 mL of saliva was easily obtained. Some of the subjects found saliva collection to be offensive, whereas other subjects were more comfortable giving a saliva sample than a venous blood sample. The plasma was immediately separated by centrifugation from erythrocytes and both plasma and saliva were stored at −70°C until extraction.

The procedure for extraction and radioimmunoassay of substance P was that described by Yanaihara et al. (6,7). It involves slow addition of 2 mL of cold acetone to 1 mL of plasma or saliva while vortexing. The resulting mixture was centrifuged and the supernatant was decanted. Petroleum ether (4 mL) was added to the supernatant and the components were thoroughly mixed by vortexing with the phases then separated by centrifugation at 760 *g*. The upper ether layer was removed and discarded and the lower aqueous layer was evaporated to dryness under nitrogen at 37°C. The residues were then stored at −20°C for radioimmunoassay which started with combining the plasma or saliva extract, rabbit–anti-substance P and ^{125}I-labeled substance P. The mixture was vortexed and incubated overnight at 4°C. Phase separation was accomplished by the addition of an equal volume of saturated ammonium sulfate in the presence of carrier γ-globulin. This mixture was then also vortexed vigorously, allowed to stand for 15 min, and centrifuged at 760 *g* for 10 min, after which the supernatant fluid was decanted and the pellet blotted to remove extraneous fluid and counted for ^{125}I. Maximum binding, nonspecific binding, and values for the substance P standard curve (39–1250 pg/mL) were determined at the same time. All solutions for this assay were made in 0.05 M boric acid buffer containing bovine serum albumin (0.25%), peptone (0.25%), and merthiolate (0.0005%). Substance P levels were calculated from calibration curves that were obtained by plotting the logit transformation of the extent of binding against the log of the stated concentration of the authentic standards. The extent of binding was defined as the ratio of the counts per minute to the counts per minute of the maximum binding (both corrected for the nonspecific binding). Substance P levels are expressed per milligram protein.

Anti-substance P used in the radioimmunoassays was supplied by Incstar Corp., Stillwater, Minn. It was found to be highly selective to detect substance P with negligible cross-reactivity with several other peptides. For example, anti-substance P has 100% cross-reactivity with standard substance P and <0.002% cross-reactivity with other mammalian (neurokinin A, neurokinin B) and nonmammalian (eledoisin, physalaemin) tachykinins structurally related to substance P. It has <0.002% cross-reactivity with the opioid peptides methionine-enkephalin and leucine-enkephalin, and 0.008% cross-reactivity with β-endorphin. All of these observations suggest that the present radioimmunoassay was highly selective for substance P. A method has been described in the literature in which microgram quantities of biopeptides were separated by high-pressure liquid chromatography and detected by ultraviolet light at 254 nm (8). This method was not sensitive enough to detect quantities of substance P and opioid peptides that occur in body fluids unless separation by high-pressure liquid chromatography was coupled to sensitive radioimmunoassays. There is a limitation on the volume of human saliva or plasma available for analysis. As a highly sensitive anti-substance P is available, the intermediate step of high-pressure liquid chromatography separation of extracted biopeptides is unnecessary. Therefore, the radioimmunoassay was directly applied to extracted biopeptides in the present studies.

To determine the presence of substance P in healthy human volunteers, saliva (18 mL) was pooled from volunteers and extracted for substance P as previously described. The dried extract was then resuspended in the radioimmunoassay buffer, diluted serially, and assayed in the same manner as the standard substance P. Total plasma or saliva protein was determined by the method of Lowry et al. (9). Student's *t*-test was used to analyze the difference between the groups and $P < 0.05$ was considered to be statistically significant.

Results

The dilution curves for the saliva extract and the substance P standard curve prepared in buffer are

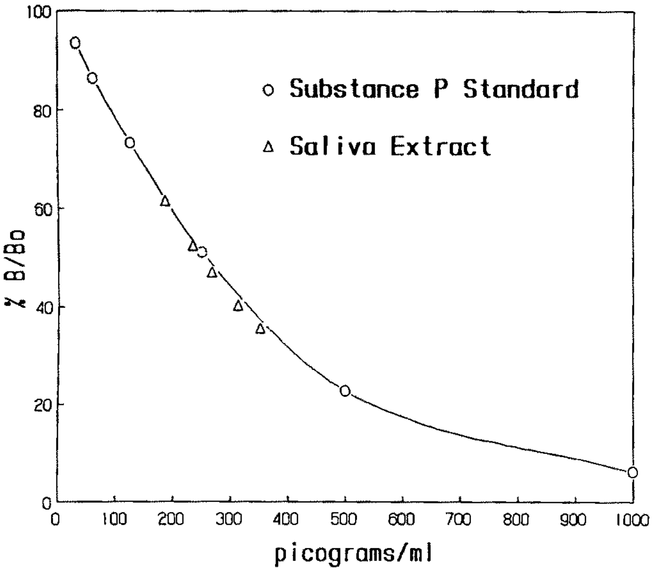

Figure 1. Correlation between saliva extract and substance P dilution curves.

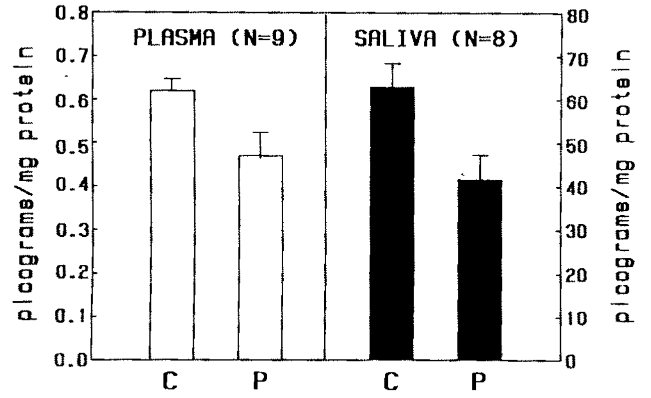

Figure 2. Comparison of mean (±SEM) levels of immunoreactive substance P in healthy volunteers (C) and chronic pain patients (P).

presented in Figure 1. The dilution curve for the saliva extract was indistinguishable from the substance P standard curve, implying that the substance P-like compound in saliva extract is immunologically identical to substance P. Plasma and saliva immunoreactive substance P values from healthy volunteers and chronic pain patients are presented in Figure 2. There were no significant differences in the mean substance P levels of seven patients who took drugs and two patients who did not receive any drugs. Therefore, these nine patients were pooled into one group of chronic pain patients for analysis. The levels of substance P expressed per milligram of protein were significantly greater in saliva than in plasma ($P < 0.01$) both in healthy volunteers and in chronic pain patients. The total protein in the plasma and saliva of healthy volunteers did not differ from the corresponding protein levels of chronic pain patients (Table 1). However, substance P levels in both saliva and plasma, when expressed per milligram of protein, were significantly less ($P < 0.05$) in chronic pain patients than in healthy volunteers. In all patients and volunteers, levels of immunoreactive substance P measured in saliva were markedly higher than levels measured in plasma.

Discussion

Substance P is widely distributed in the central nervous system (10). Its specific function is unclear. It is probably a neurotransmitter with varied functions, some of which may be paradoxical. Its synthesis, release, and metabolism may be influenced by several physiologic and pathological events in the body. Plasma levels of substance P are elevated in some disease states (11) and lowered in others (12). Substance P levels have been studied in CSF, in trigeminal ganglion complex, in several sites within the brain (with highest concentrations in substantia nigra of the midbrain), in substantia gelatinosa of the spinal cord dorsal horn, and in plasma. Collection of samples for substance P assays in CSF and, to a lesser extent, plasma involve relatively invasive procedures that may be unacceptable to some chronic pain patients. Therefore, the search for a noninvasive, simple, and reliable technique to assay substance P in a peripheral body fluid appeared relevant and justified. To that end, saliva was considered for analysis. A large volume of saliva from a pool of healthy human volunteers was also collected and processed for the extraction of substance P. The extract was diluted serially in the same manner as the standard substance P. There was excellent correlation of the dilution curve between the known substance P standard and the saliva extract. This strongly suggests that substance P is indeed present in saliva.

Mean immunoreactive substance P levels (per milligram of protein) were ~100 times higher in the saliva than in the plasma of both patients with chronic pain and healthy volunteers. This is partly explained by the higher total protein content in plasma than in saliva. However, substance P levels were also consistently higher in saliva of both groups when expressed per milliliter. The substance P-like immunoreactivity extracted from 1 mL of saliva gives a binding response in the radioimmunoassay in the midrange of the standard curve. This is the most linear region of the curve and therefore the area where the most reliable results would be obtained. Larger volumes of plasma or CSF would need to be extracted to gain the same response. Saliva may be

Table 1. Mean (±SEM) Levels of Plasma and Saliva Immunoreactive Substance P and Total Protein in Healthy Volunteers and Chronic Pain Patients

	Plasma (n = 9)			Saliva (n = 8)		
	SP (mg/mL)	Total protein (mg/mL)	SP (pg/mg)	SP (pg/mL)	Total protein (mg/mL)	SP (pg/mg)
Healthy volunteers	62.47^a	101.08^b	0.62^c	151.04^a	2.58^b	62.88^c
	±3.24	±1.63	±0.03	±17.6	±0.35	±6.43
Chronic pain patients	47.41^a	102.29^b	0.47^c	230.76^a	5.99^b	41.68^c
	+5.36	±2.16	±0.06	±69.06	±1.82	±6.46

SP, substance P.
[a] Differences were significant at $P < 0.05$.
[b] Differences were not significant at $P < 0.05$.
[c] Differences were significant at $P < 0.05$.

the preferred body fluid in which to measure substance P in chronic pain patients because of the higher substance P levels in saliva and the fact that CSF and peripheral blood collection in some chronic pain patients may be inappropriate. In the group of chronic back pain patients we studied, mean immunoreactive substance P levels in plasma and saliva were significantly lower than in healthy volunteers. These results correspond favorably with the results of the CSF study of Almay et al. (2).

The potential significance of the findings of this study is restricted at this time. These findings may, however, prove to have clinical, economic, and biochemical implications. Clinically, there is no reliable objective marker or correlate of chronic pain. The resolution of a chronic pain syndrome or the assessment of the pain intensity of a particular syndrome is purely subjective. If our preliminary findings are substantiated, a simple noninvasive objective method may become useful in the evaluation, diagnosis, and treatment of chronic pain. It is tempting to postulate that saliva or plasma substance P may assist in differentiation of pathogenic pain from nonpathogenic (psychogenic) pain, but this claim cannot be made at this time. It is, however, interesting to note that the Almay study (2) showed the CSF substance P levels were lowest in patients with neurogenic pain compared with patients with idiopathic pain and healthy volunteers. The possible economic significance of having an objective marker for chronic pain would be considerable as billions of dollars are spent annually on chronic pain patients (particularly injured workers) using unreliable subjective measures of chronic pain.

Substance P is described as a sialogogue in experimental animals (13), and substance P binding sites have been described in rat submaxillary and sublingual glands (13–15). However, there are no reports on the occurrence of substance P-like tachykinins in the saliva of experimental animals and humans. The present study is the first demonstration of the occurrence of substance P-like immunoreactivity in saliva. The observation of lower saliva and plasma levels of immunoreactive substance P in chronic pain patients than in healthy volunteers provides fascinating clues about human perception of pain. There is an interesting reciprocal homeostatic relationship about the rates of neuronal release of substance P and methionine-enkephalin in rodent cerebral slices in vitro or spinal cord in vivo (16), and substance P-induced analgesia (antinociception) could be attributed to increased release of methionine-enkephalin in the nervous system. Healthy volunteers with high saliva and plasma levels of substance P could release greater amounts of methionine-enkephalin than chronic pain patients. The threshold for pain perception may, therefore, be set at a lower level in chronic pain patients than in healthy volunteers.The reason for the low plasma and saliva levels of substance P in chronic pain patients is not known; it may be partly attributed to the differences in the rates of synthesis and metabolism of substance P in chronic pain patients and healthy volunteers.

More information on the precise role of the tachykinins in general and on substance P in particular is needed to fully understand the precise role and clinical significance of substance P in the body fluids. Ample animal data (17) exist to suggest that substance P is a transmitter of primary sensory neurons that induces marked depolarization accompanied by high-frequency spike discharges of the motoneurons. There is also evidence (18) that substance P activates the inhibitory interneurons in the spinal cord. These observations imply that substance P may have dual and antagonistic functions: acting as a nociceptive substance on some occasions and as an antinociceptive substance on other occasions. There are several factors that may initiate substance P release and inactivation. These factors may ultimately determine the specific clinical significance of our findings. Our optimistic speculation is that substance P in saliva may be a correlate of chronic pain and that these observations may be significant in the search for reliable and reproducible biological markers of chronic pain.

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Labetalol and Esmolol in the Control of Hypertension After Intracranial Surgery

Donald A. Muzzi, MD, Susan Black, MD, Thomas J. Losasso, MD, and Roy F. Cucchiara, MD

MUZZI DA, BLACK S, LOSASSO TJ, CUCCHIARA RF. Labetalol and esmolol in the control of hypertension after intracranial surgery. Anesth Analg 1990;70:68–71.

The postoperative course of patients emerging from general anesthesia after intracranial surgery is frequently complicated by hypertension. This study examined the comparative efficacy of esmolol and labetalol in treating increases in blood pressure during emergence and recovery from anesthesia after intracranial surgery.

Both esmolol and labetalol were equally effective in controlling systolic blood pressure on emergence and in the recovery room in patients undergoing intracranial surgery. However, decreases in heart rate were significantly more frequent in the immediate postoperative period in patients given labetalol. An increase in blood pressure after intracranial surgery appears to be a transitory phenomenon adequately treated with a short-acting antihypertensive agent such as esmolol.

Key Words: SYMPATHETIC NERVOUS SYSTEM, PHARMACOLOGY—esmolol, labetalol. BLOOD PRESSURE, HYPERTENSION—postoperative. ANESTHESIA, NEUROSURGICAL.

The postoperative course of patients emerging from general anesthesia after intracranial surgery is frequently complicated by the occurrence of hypertension (1). This clinical open-label randomized study examines the comparative efficacy of labetalol and esmolol in treating increases in blood pressure during emergence and recovery from general anesthesia after intracranial surgery. It also evaluates the usefulness of these drugs in the immediate postoperative period based on the clinical needs of this group of patients.

Methods

After institutional review board approval, 55 patients scheduled for an elective craniotomy for removal of an intracranial tumor were enrolled in the study. All patients were monitored with a V_5 lead of the electrocardiogram, pulse oximeter, and an indwelling arterial catheter for blood pressure measurements. Respiratory monitoring included mass spectrometry to measure inspired and expired anesthetic and respiratory gases.

Patients were excluded from the study if they were being treated with β-adrenergic blocker therapy before surgery. Other exclusion criteria included sinus bradycardia, greater than first degree heart block, bronchial asthma, or history of congestive heart failure.

General anesthesia was induced with 4–5 mg/kg of thiopental and 2–4 μg/kg of fentanyl. Tracheal intubation was facilitated with 0.2 mg/kg of vecuronium. General anesthesia was maintained with isoflurane, nitrous oxide, and fentanyl (total fentanyl dose was 6–8 μg/kg). Muscle relaxation, maintained with vecuronium, was reversed with 0.06 mg/kg of neostigmine and 0.0125 mg/kg of glycopyrolate at the conclusion of surgery.

Emergence from general anesthesia was defined as the period beginning when the volatile anesthetic was discontinued and ending when the trachea was extubated. Hypertension was defined as an increase in systolic blood pressure (SBP) of ≥20% above each patient's average SBP as determined preoperatively on the ward. The beginning of the recovery-room period was defined as the period immediately after

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extubation. Hypotension was defined as a decrease in SBP of ≥20% below each patient's average ward value. Bradycardia was defined as a decrease in heart rate of ≥20% below the average ward value of each patient.

The patients were randomized into two groups and received either esmolol or labetalol if their SBP on emergence was ≥20% above average ward SBP. Extubations were performed in the operating room.

The patients in the esmolol group (n = 25) received a loading dose of 500 μg/kg followed by an infusion of 50–300 $\mu g \cdot kg^{-1} \cdot min^{-1}$ to maintain SBP within 20% of average ward preoperative values. Esmolol was discontinued 10 min after extubation and before transport to the recovery room.

The patients in the labetalol group (n = 25) were given incremental doses of 0.25, 0.5, 0.75, and 1.00 mg/kg to maintain SBP within 20% of average preoperative ward values. Approximately 3 min was allowed between each dose of labetalol. Thus, a maximum dose of 2.5 mg/kg of labetalol could have been administered. Labetalol was not given after extubation.

If the blood pressure was not controlled with labetalol or esmolol, sodium nitroprusside was added for blood pressure control.

Demographics and perioperative hemodynamic data were analyzed utilizing χ^2-tests. Results were considered statistically significantly different if the P value was ≤0.05.

Results

Fifty of the 55 patients (91%) enrolled in the study became hypertensive during their emergence from anesthesia.

There was no statistically significant difference between the esmolol and labetalol treatment groups with respect to age, sex, weight, preoperative medication, or medical history. One patient in the labetalol and one patient in the esmolol group had a history of hypertension. For preoperative blood-pressure control the patient in the labetalol group was treated with captopril and the patient in the esmolol group was treated with hydrochlorothiazide.

The average (mean ± SD) ward SBP for patients in the esmolol and labetalol groups was 123 ± 11 and 122 ± 13 mm Hg, respectively. Treatment with esmolol or labetalol was initiated during emergence when SBP increased to 20% above the average ward value. For the esmolol and labetalol groups, the average SBP when therapy was initiated was 148 ± 13 and 147 ± 15 mm Hg, respectively. Both average ward SBP and SBP when antihypertensive therapy was initiated were not significantly different between treatment groups.

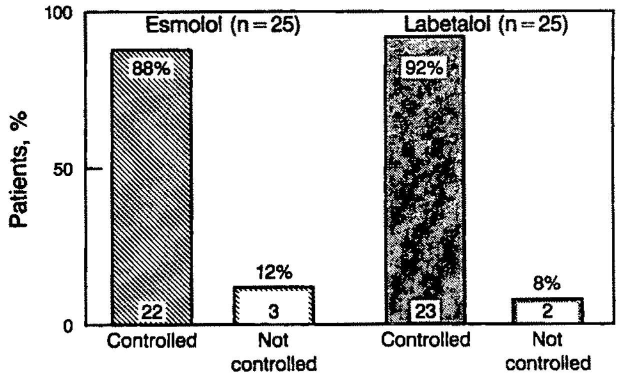

Figure 1. Efficacy of esmolol and labetalol in controlling hypertension.

There was no difference in the effectiveness of esmolol and labetalol in the control of hypertension between the two groups. During emergence from general anesthesia esmolol effectively controlled hypertension in 22 of 25 patients (88%) and labetalol was effective in controlling hypertension in 23 of 25 (92%) (Figure 1). The mean esmolol dosage required for control of hypertension was 160 $\mu g \cdot kg^{-1} \cdot min^{-1}$ by infusion with a range from 50 to 300 $\mu g \cdot kg^{-1} \cdot min^{-1}$. The mean labetalol dosage required for control of hypertension was 0.97 mg/kg total dose with a range of 0.25–2.50 mg/kg. Pharmacologic intervention became necessary for the treatment of hypertension from 5 to 25 min before extubation.

There was no difference in the frequency of hypertension in the recovery room between the two groups. In the recovery room hypertension occurred in eight of 25 patients in the labetalol group (32%) and in nine of the 25 patients in the esmolol group (36%) (P = 0.77). The mean time to onset of hypertension in the recovery room was 18 min in the labetalol group and 27 min in the esmolol group.

There was no difference in the frequency or severity of hypotension in the recovery room between the esmolol and labetalol groups. Hypotension in the recovery room occurred in four of 25 patients in the labetalol group (16%) and in three of 25 patients in the esmolol group (12%) (P = 0.68). Treatment-induced hypotension during emergence occurred in one patient in the esmolol group and none of the patients in the labetalol group.

There was no difference in the average (mean ± SD) ward heart rate between the esmolol and labetalol groups, 76 ± 9 and 76 ± 7 beats/min, respectively. There was no difference in the incidence or severity of bradycardia during emergence from general anesthe-

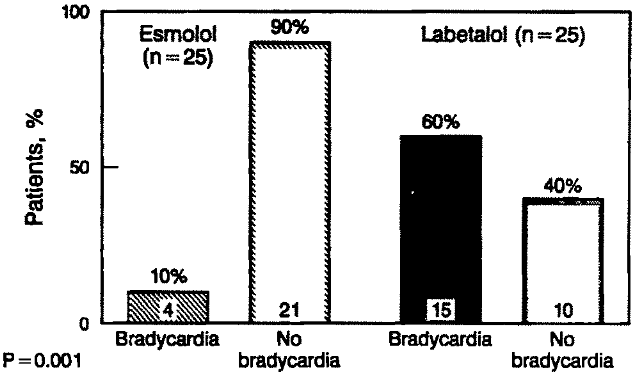

Figure 2. Incidence of bradycardia in the recovery room.

sia between the two groups. Four of the 25 patients in the labetalol group (16%) and eight of the 25 patients in the esmolol group became bradycardic during emergence from anesthesia (32%) ($P = 0.19$).

The incidence of bradycardia in the recovery room was statistically significantly different between the two groups. Bradycardia occurred during the recovery period in 15 of 25 patients in the labetalol group (60%) and in four of 25 patients in the esmolol group (10%) ($P = 0.001$) (Figure 2). In the 15 patients in the labetalol group who became bradycardic in the recovery room, the average bradycardic heart rate was 56 beats/min with a range from 40 to 62 beats/min.

There was no difference in the dose of labetalol between the patients who developed bradycardia and those patients who did not develop bradycardia. The mean (±SD) dose of labetalol in the patients who developed bradycardia versus those who did not was 0.99 (±0.70) and 1.05 (±0.66) mg/kg, respectively.

Discussion

Hypertension is a significant clinical problem in neurosurgery during emergence from general anesthesia and in the recovery room. Proper anesthetic management includes perioperative maintenance of hemodynamic stability. Two studies have associated perioperative hypertension or tachycardia with an increased incidence of cerebral hemorrhage and myocardial ischemia (2,3). The use of a short-acting β-adrenergic blocking agent, esmolol ($t_{1/2}$ = 9 min), effectively blunts hypertension in patients after intracranial surgery (1). Labetalol is a mixed α- and β-adrenergic blocker with a longer duration of action ($t_{1/2}$ = 5 h). It too effectively controls perioperative hypertension in nonneurosurgical patients (4). Labetalol may offer advantages in the control of hypertension well into the postoperative period. However, the desirability of antihypertensive action in the postoperative period when the level of stimulation is dramatically decreased is not clear. The hemodynamic response to increased intracranial pressure is hypertension and bradycardia. Use of a long-acting antihypertensive agent with α- and β-adrenergic blocking effects may confuse the interpretation of hemodynamic parameters in neurosurgical patients recovering from anesthesia. A shorter acting agent such as esmolol may suffice in the treatment of postoperative hypertension.

Esmolol and labetalol have no significant effect on intracranial pressure or cerebral blood flow (5–7). Their apparent lack of effect on cerebrovascular dynamics and intracranial pressure makes them an attractive choice for management of hypertension in neurosurgical patients.

In the present study there was no difference in the occurrence of hypertension in the recovery room between the esmolol and labetalol groups. This implies that a short-acting agent suffices in the treatment of emergence and postoperative hypertension in neurosurgical patients undergoing tumor excision. Commonly used short-acting antihypertensive agents for the management of hypertension during emergence from general anesthesia include intravenous sodium nitroprusside and nitroglycerin. Many patients are given these drugs before the end of intracranial surgical procedures, whereas others receive them for hypertension that develops in the immediate postoperative recovery period. Potential drawbacks to the use of nitroprusside and nitroglycerin in neurosurgical patients include cerebrovasodilatation with elevation of intracranial pressure, pulmonary venous admixture, undesirable decrease in diastolic blood pressure, reflex tachycardia, and lability in blood pressure while adjusting the dose or while moving the patient (8,9).

Leslie et al. (4) reported a mean dose of 1.38 mg/kg of labetalol to control hypertension after nonneurosurgical operations. The mean dose of labetalol required for control of hypertension in our patients was 0.97 mg/kg. In patients having craniotomies for tumors, as in the present study, the dose of labetalol required to control hypertension on emergence appears to be large enough to cause bradycardia when surgical stimulation has ceased. However, comparison of the dose of labetalol administered to patients who developed bradycardia with that of patients who did not develop bradycardia failed to demonstrate a significant difference in the dose of labetalol administered. The incidence of bradycardia was significantly higher in the immediate postoperative period in our patients who received labetalol. We believe this is related to the large doses of labetalol needed to control hypertension during the stimulation of emergence from general anesthesia yielding negative chronotropic effects when stimulation is at low levels later in the recovery room.

As the incidence of hypotension was not statistically different between the esmolol and labetalol groups, the bradycardia was not generally hemodynamically significant. However, the occurrence of bradycardia in these patients requires close and perhaps prolonged observation in the recovery room.

The 91% incidence of hypertension (50 of 55 patients) after intracranial surgery in this study is consistent with the findings by Gibson et al. (1). Our definition of hypertension as an increase in SBP of ≥20% above average ward SBP is in agreement with previous studies regarding control of hypertension during and after surgery with general anesthesia (4,10–14). Previous reports have shown the dosage regimens for esmolol and labetalol used in this study to be effective in decreasing SBP approximately 15% in patients developing hypertension after nonneurosurgical operations (4,10). In the present study esmolol and labetalol effectively controlled hypertension during emergence and recovery from anesthesia in patients after intracranial surgery.

Only two patients enrolled in this study had a history of chronic hypertension. We cannot, therefore, evaluate the efficacy of short-acting antihypertensive agents in treating emergence hypertension in chronic hypertensive patients based on our data. It is possible that esmolol may not provide adequate blood pressure control in chronic hypertensive patients during emergence from general anesthesia and in the postoperative period.

The two most prevalent theories of the cause of emergence hypertension after any surgical procedure include increased blood levels of catecholamines and increased sympathetic stimulation (11,12). The efficacy of esmolol, in the treatment of postoperative hypertension, is consistent with these theories. Both esmolol and labetalol were effective in controlling hypertension after intracranial surgery. However, the incidence of bradycardia was greater in patients treated with labetalol. Hypertension after intracranial surgery appears to be a frequent but transitory phenomenon adequately treated with a short-acting antihypertensive agent such as esmolol. Esmolol is an attractive choice as it lacks significant effects on intracranial pressure and cerebral blood flow (7).

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1990;70:72–5

Epidural and Intravenous Fentanyl Infusions Are Clinically Equivalent After Knee Surgery

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LOPER KA, READY LB, DOWNEY M, SANDLER AN, NESSLY M, RAPP S, BADNER N. Epidural and intravenous fentanyl infusions are clinically equivalent after knee surgery. Anesth Analg 1990;70:72–5.

The management of postoperative pain with continuous epidural fentanyl infusion was compared with continuous intravenous fentanyl infusion. In a randomized, double-blind protocol we prospectively studied 20 patients undergoing repair of the anterior cruciate ligament of the knee. The quality of analgesia and the incidence of side effects were documented. Compared with patients receiving continuous intravenous fentanyl infusion, at 18 h postoperatively patients given continuous epidural fentanyl infusion reported similar pain scores both at rest (22 ± 25 vs 27 ± 21, $P = 0.52$) and with ambulation (59 ± 18 vs 56 ± 22, $P = 0.82$). Plasma fentanyl levels were 1.8 ± 0.4 and 1.7 ± 0.4 ng/mL ($P = 0.91$) for the intravenous and epidural groups, respectively. There were no significant differences in the incidence of nausea, pruritus, or urinary retention. There was no respiratory depression in either group. We conclude that when compared with continuous intravenous fentanyl infusion, continuous epidural fentanyl infusion offers no clinical advantages for the management of postoperative pain after knee surgery.

Key Words: ANESTHETIC TECHNIQUES, EPIDURAL—fentanyl. ANALGESICS, FENTANYL. PAIN, POSTOPERATIVE.

The management of postoperative pain can be improved with the use of epidural opioids (1,2). The majority of clinical publications deal with the use of morphine (3). The benefits sought by using other opioids are greater analgesia or a lower incidence of side effects, or both. Fentanyl, with its rapid onset and short duration of action, has been recommended for use as a continuous epidural infusion (4). Recent studies have suggested that such infusions have the advantage of achieving analgesia in less time than epidural morphine (5,6). Epidural opiate analgesia, however, is not without an element of risk and an incidence of side effects (1). To date there have been no controlled clinical comparisons between continuous intravenous (IV) and epidural fentanyl infusions. The purpose of this study was to make this comparison and determine whether there are advantages to the epidural route for postoperative pain management.

Methods

With the approval of our institutional human investigation committee and the written informed consent of patients (University Medical Center, Seattle, Wash.), a prospective study was undertaken of 20 consecutive patients presenting for repair of the anterior cruciate ligament of the knee. All patients were ASA physical status I, ranging from 16 to 44 yr of age. The surgery was performed by the same orthopedist. For their operative procedure, patients were given an epidural anesthetic established by injecting 2% lidocaine or 0.5% bupivacaine into a catheter placed at either the L2-3 or L3-4 interspace. Sedation was provided at the discretion of the anesthesiologist.

In a double-blind protocol, patients were randomly assigned to one of two groups. The "EP-fentanyl" group received an epidural infusion of

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fentanyl at 100 μg/h (2 mL/h) and a placebo IV infusion of normal saline at 2 mL/h. The "IV-fentanyl" group received an IV fentanyl fusion at 100 μg/h (2 mL/h) and a placebo epidural infusion of normal saline at 2 mL/h. Approximately 1 h before the completion of surgery, a 100-μg fentanyl loading dose was administered and the respective IV and epidural infusions were initiated.

Supplemental analgesia was available as needed for each patient to establish comfort at rest and to permit ambulation without severe pain. Upon patient request, a ward nurse administered coded medications such that EP-fentanyl patients received 50 μg of fentanyl (2 mL) through the epidural catheter and 2 mL normal saline through the IV catheter; IV-fentanyl patients received 50 μg of fentanyl (2 mL) through the IV catheter and 2 mL of normal saline through the epidural catheter. No other opiates or sedatives were administered either systemically or epidurally.

At 18 h postoperatively, a 10-mL venous blood sample was obtained from a peripheral vein in a limb other than that bearing the fentanyl infusion; the plasma was separated and stored at −20°C until plasma fentanyl concentrations were measured by radioimmunoassay (7). Further, the administration of supplemental analgesic boluses was noted. Patients assessed their incisional pain both at rest and upon ambulation using a visual analogue scale (VAS: 100-mm line with the left end labeled "No Pain" and the right end labeled "Severe Pain"). Finally, the occurrence of side effects was recorded using the following scales: nausea and pruritus (0 = none; 1 = mild, no medications requested; 2 = moderate, medications requested and effective; 3 = severe, medications administered but not effective); urinary retention (0 = none; 1 = hesitancy; 2 = one or two "in and out" bladder catheterizations needed; 3 = >2 "in and out" bladder catheterizations or a Foley catheter required).

Statistical analysis of the continuously distributed variables (age, VAS scores, and serum fentanyl concentrations) was performed using the Mann–Whitney test (8). Interval data for side effects were coded to form two tables for the binary outcome: clinical intervention versus no clinical intervention. Analysis of these data was by the Fisher–Irwin exact test. A two-tailed 5% critical level of significance was assigned for all comparisons. Values are reported as the mean, median ± standard deviation, and 95% confidence intervals (CIs) of group mean differences.

Results

There were no significant differences in the ages of the patients in the EP-fentanyl and IV-fentanyl groups (26, 24 ± 8 vs 28, 26 ± 9 yr; $P = 0.60$, 95% CI = −6, 9). Patients in both the EP-fentanyl and IV-fentanyl groups requested approximately the same number of supplemental analgesic boluses (2.5, 2.2 ± 1.8 vs 2.7, 2.0 ± 2.8; $P = 0.82$, 95% CI = −2, 2).

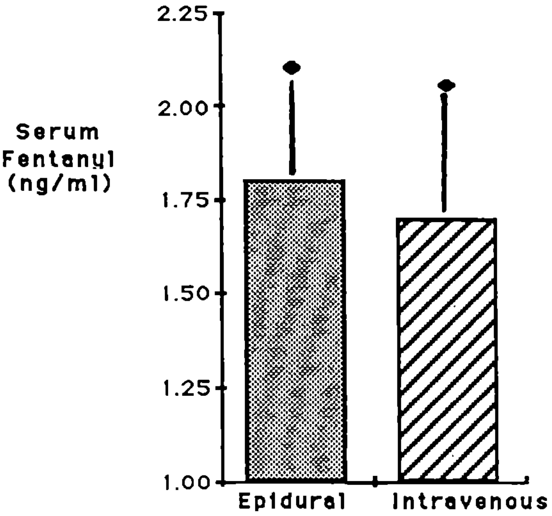

Figure 1. Mean plasma fentanyl concentrations ± SD at 18 h postoperatively. The IV and epidural infusions were initiated approximately 1 h before the completion of surgery along with a 100-μg fentanyl loading dose.

At 18 h postoperatively patients in both the EP-fentanyl and IV-fentanyl groups had similar plasma fentanyl concentrations (Figure 1), and reported similar pain scores both at rest and upon ambulation (Figure 2). Patients in both groups reported a similar incidence of side effects (Figure 3). There was no clinically evident respiratory depression (a respiratory rate of <8 as detected by a nurse at hourly checks).

Discussion

Among the reports claiming advantages of continuous epidural fentanyl infusion for managing postoperative pain, there is little information with respect to either the pain control achieved or the incidence of side effects compared with continuous IV fentanyl infusion. One report comparing epidural to IV fentanyl administration found no detectable differences in overall pain relief between the two groups (9). However, in that study, patients self-administered a variable amount of fentanyl by means of patient-controlled pumps while recovering from a variety of surgical procedures.

Patients presenting for repair of the anterior cruciate ligament of the knee represent a healthy surgical population undergoing a single procedure that

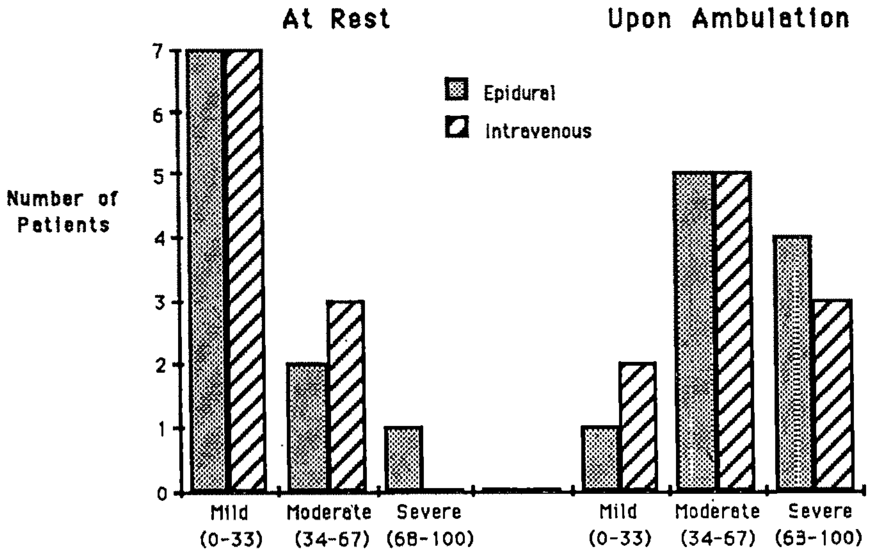

Figure 2. Distribution of pain scores using a visual analogue scale, a 100-mm line with the left end labeled "No Pain" and the right end labeled "Severe Pain."

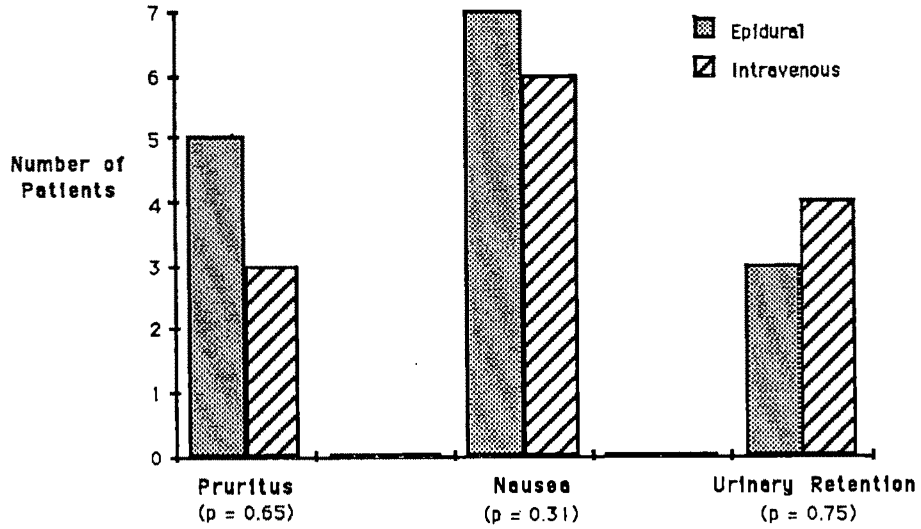

Figure 3. Incidence of side effects requiring medical intervention.

causes severe pain. The relatively young age of these patients tends to minimize previously described pain modifiers such as old age, chronic pain, and learned helplessness (10).

The ability of lipophilic opiates to spread within the cerebrospinal fluid may be limited (11). Hence, when infusing lipophilic opiates into the epidural space, it may be important to place the epidural catheter in the area of maximum nociceptive input. Given the L3-4 dermatomal innervation of the knee, the epidural catheter was placed at the L2-3 or L3-4 interspace, thereby eliminating the need to infuse the fentanyl in large volumes.

The identical continuous infusions of fentanyl used in this study allowed a comparison of the quality of analgesia achieved by the epidural and IV routes of administration. A stable plasma fentanyl concentration is achieved within 10 h of instituting either IV (12,13) or epidural infusions (14). At 18 h postoperatively, compared with the IV-fentanyl group, EP-fentanyl patients reported similar pain relief and experienced a similar incidence of side effects. It should be recognized that this trial, with its small sample size, is limited in its power to detect small differences.

Analysis of epidural administration is complicated by systemic uptake. Previous calculations have shown that the proportion of an epidural dose transferred across the dura mater can vary from up to 20% for morphine (low lipid solubility) to 0.2% for buprenorphine (high lipid solubility) (15). Our results are consistent with the recent report that intrathecal opioid potency is inversely correlated with lipophilicity, so that the most lipid soluble opiates produce the least potent spinally mediated analgesia (16). The finding that satisfactory analgesia was associated with an adequate plasma level irrespective of the route of administration is in agreement with previous clinical studies (9,17). Although our findings do not preclude a neuraxial component contributing to pain relief in those patients receiving a continuous epidural fentanyl infusion, the results suggest that systemic uptake is of major importance.

In summary, we have shown that after anterior cruciate ligament repair, a continuous epidural fentanyl infusion provides a similar degree of pain relief and causes a similar incidence of side effects relative to continuous IV fentanyl infusion.

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Impaired Epidural Analgesia After Dural Puncture with and Without Subsequent Blood Patch

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We carried out a retrospective assessment of epidural analgesia in 46 parturients who had a previous dural puncture. Of 29 women who had both dural puncture and blood patch previously, only 59% had an uncomplicated successful second epidural anesthetic. Of 17 parturients who had dural puncture but no blood patch previously, only 65% had an uncomplicated successful subsequent epidural anesthetic. In comparable groups of parturients without previous dural puncture, 88%–92% had successful epidural analgesia. The data suggest that dural puncture may lead to impaired epidural analgesia subsequently. Epidural blood patch after dural puncture did not lead to any further decrease in the rate of good analgesia with subsequent epidural anesthetics. Parturients who request epidural analgesia and who have had previous dural puncture with or without blood patch should be informed about the 35%–40% chance of poor epidural analgesia.

Key Words: ANESTHETIC TECHNIQUES, EPIDURAL. ANESTHETIC TECHNIQUES, SPINAL—headache.

Headache is one of the most common complications after intentional or inadvertent dural puncture. Epidural blood patch is an effective therapy and is often used for treatment of persistent headache after dural puncture (1–4). There are conflicting case reports in the literature about the success of epidural analgesia after epidural blood patch. Sixteen patients from five different institutions have been reported to have had successful epidural analgesia/anesthesia after a previous blood patch (3–7). Crawford (7) and Rainbird and Pfitzner (8) have reported restricted upward spread of analgesia or "missed segment" in three patients after blood patch. These case reports do not allow one to determine the incidence of impaired epidural analgesia after blood patch. Also, the effect of dural puncture without blood patch on subsequent epidural analgesia has not been assessed previously. To determine the effects of dural puncture with and without blood patch on subsequent epidural analgesia, we examined the clinical courses among parturients who had two epidural anesthetics at the Winnipeg Women's Hospital and at St. Boniface General Hospital from 1975 to 1987.

Methods

We reviewed 204 medical records of parturients who had inadvertent dural puncture during insertion of epidural catheters or who had significant headache in the postpartum period. From these records we identified 46 parturients who had a second epidural anesthetic after dural puncture with or without a subsequent epidural blood patch. The parturients delivered their infants in either Women's Hospital or St. Boniface General Hospital between 1975 and 1987. The two hospitals are located in Winnipeg, Manitoba, Canada, serve as the tertiary referral hospitals for a population of 1.5 million, and also function as community hospitals for women in the adjacent neighborhoods. The Departments of Anesthesia in the two hospitals provide 24-h coverage with an anesthesiologist on duty in each hospital at all times. Epidural

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anesthetics are performed by either anesthesia residents under supervision or the attending anesthesiologist.

For comparison, we reviewed the data on epidural anesthesia from an Obstetric Anesthesia Follow-up Program at the Winnipeg Women's Hospital from 1975 to 1983. For the Anesthesia Follow-up Study, a specially trained anesthesia nurse (the same individual throughout the 9-yr period) reviewed the parturients' hospital charts and interviewed those who received an anesthetic to determine the degree of analgesia and identify any complications that may have been related to anesthetic procedures. A full description of the patient population and study methods of the follow-up study has been published previously (9).

The follow-up study provided the success and failure rate of epidural anesthesia from Women's Hospital for parturients having their first or second epidural anesthetic without previous dural puncture or other complications. Epidural analgesia was judged a failure or inadequate if there was persistent pain after normal doses of local anesthetics or failure to achieve analgesia above the T-10 level during cesarean section. The anesthesia residents rotate frequently between the two hospitals, and the success rates of epidural anesthesia in the two hospitals are comparable.

The success rates of epidural analgesia among parturients who were having their first epidural anesthetic, parturients who had previous successful epidural anesthesia, parturients who had previous dural puncture, and parturients who had previous dural puncture and epidural blood patch were compared by χ^2 analysis. The ages of parturients and the time intervals between the first and second epidural anesthetics for the different groups were compared by unpaired Student's *t*-test. $P < 0.05$ was used as the level of significance.

Results

Forty-six parturients had a second epidural anesthetic after dural puncture. Of these, 29 had an epidural blood patch, and the other 17 were managed with fluid, analgesics, and bed rest. In subsequent pregnancies, 23 of these parturients received epidural analgesia for vaginal deliveries, and 23 had epidural anesthesia for cesarean section deliveries. The success rate of the second epidural anesthetic in these parturients was compared with the success rate of epidural anesthesia in three other groups of parturients, namely (a) 928 parturients who had good analgesia from their first epidural anesthetic and had a subsequent epidural anesthetic; (b) 5691 primigravid patients having their first epidural anesthetic; and (c) 1973 multigravid patients having their first epidural anesthetic after previous delivery without epidural analgesia. The rates of successful epidural analgesia among the five groups of parturients are shown in Table 1.

Table 1. Incidence of Successful Epidural Analgesia Among Different Groups of Parturients

Patient characteristics	No. of patients	Incidence of successful epidural analgesia (%)
Previous dural puncture and epidural blood patch	29	59[a]
Previous dural puncture only	17	65[a]
Previous uncomplicated epidural analgesia/anesthesia	928	90
First epidural analgesia in primigravidae	5691	92
First epidural analgesia in multigravidae	1973	89

[a] $P < 0.05$ compared with parturients without previous dural puncture.

Of the 29 parturients who had dural puncture and blood patch previously, five had poor analgesia due to missed segments or restricted spread of analgesia, three required large doses of local anesthetics to obtain adequate anesthesia for cesarean section (specifically, 35, 35, and 37 mL of carbonated 1.75% lidocaine hydrochloride solutions compared with the usual doses of 15–20 mL of the same solution), and in four instances the attending anesthesiologist abandoned epidural anesthesia and administered general anesthesia. Seventeen of the 29 parturients had uncomplicated good epidural analgesia for a success rate of 59% in this group.

Of the 17 women who had dural puncture but who did not receive an epidural blood patch, six had poor analgesia due to missed segments or restricted spread of analgesia. Four of these six women required general anesthesia to complete the cesarean section. Eleven had good epidural analgesia for a success rate of 65% in this group.

There was no significant difference in average age of the patients and the average time between the dural puncture and the second epidural anesthetic, between those who had good analgesia and those who did not (Table 2).

Among 928 parturients who had a second epidural anesthetic after a successful and complication-free first epidural anesthetic, the success rate was 90%. Among the primigravidae, 92% had good analgesia during their first epidural anesthetic; 89% of multi-

Table 2. Comparison of Parturients Who Had Good Analgesia Versus Parturients Who Had Poor Analgesia by Time Interval Between Epidural Anesthetics and by Age

Course of second epidural analgesia	Time interval (mo)	Age (yr)
A. Parturients who had previous dural puncture and blood patch (n = 29)		
Good analgesia	33 ± 13	27 ± 4
Poor analgesia	33 ± 12	25 ± 5
B. Parturients who had previous dural puncture only (n = 17)		
Good analgesia	24 ± 14	26 ± 3
Poor analgesia	25 ± 5	22 ± 5

Values are mean ± SD.

gravidae had good analgesia when they received their first epidural anesthetic after one or more previous deliveries.

Parturients who had dural puncture and parturients who had both dural puncture and epidural blood patch had lower success rates in subsequent epidural analgesia compared with parturients who did not have previous dural puncture. Epidural blood patch did not appear to cause any further decrease in rate of good analgesia with subsequent epidural anesthetics after dural puncture.

Of the 46 parturients who had dural puncture, one had poor analgesia in her first epidural anesthetic, and four had recorded technical difficulties related to insertion of a catheter into the epidural space. None of these 46 women had a dural puncture during the subsequent insertion of an epidural catheter.

Discussion

Epidural blood patch can cure post dural puncture headache immediately and effectively. With the initial reports about the success of epidural blood patch therapy, concern about adverse effects on subsequent epidural analgesia was expressed (10). Previous case reports indicated that either success or failure of epidural analgesia might occur in subsequent epidural anesthetics after dural puncture and epidural blood patch (3–7). From these anecdotal reports one cannot determine the incidence of impaired epidural analgesia after previous dural puncture with or without blood patch.

This retrospective survey showed that 41% of parturients who previously had both dural puncture and blood patch had poor analgesia with a subsequent epidural anesthetic. This is similar to the 35% failure rate of epidural anesthesia among parturients who had previous dural puncture without epidural blood patch. The similar failure rates among parturients who had epidural blood patch and among parturients who did not have epidural blood patch suggest that epidural blood patch was not a major factor in the failure of subsequent epidural anesthetics. The significant numbers of inadequate epidural analgesia may be caused by one or more factors, such as (a) previous dural puncture, (b) previous epidural anesthetics itself, (c) technical failure of the anesthesia staff, or (d) abnormalities in the epidural space of parturients who had dural puncture.

Korbon et al. (11) reported an increased rate of failed epidural anesthesia with repeated epidural anesthetics for extracorporeal shock-wave lithotripsy. However, Bray and Carrie (12) found that the incidence of unblocked segments was not affected by a previous lumbar or sacral epidural anesthetic. In the present study, during the same time period, the success rate for first or repeat epidural anesthetics was between 88% and 92% in parturients who did not have previous dural puncture. Our data indicate that a previous epidural anesthetic does not impair subsequent epidural analgesia. The observations of Korbon et al. (11) may be due to differences in surgical procedure and the much shorter time intervals between epidural anesthetics.

Our success rate for epidural analgesia in women who did not have a previous dural puncture is similar to success rates for epidural analgesia in labor and delivery reported by other investigators (13–15). There was no significant association between failures in the subsequent epidural anesthesia and any particular group of anesthesiologists or residents. These results indicate that poor epidural analgesia after dural puncture is probably not the result of prior epidural analgesia or technical failure by the anesthesiologist.

The changes in the epidural space after dural puncture and injection of blood, if any, have not been fully investigated. In an obstetric patient who died 2 days after an epidural blood patch, clots adherent to the dura in the lumbar and sacral area were observed (16). The patient in that case report (16) died suddenly, and bilateral chronic subdural hematoma in the cranium was found on postmortem examination. In a unique experimental study in Angora goats, DiGiovanni et al. (17) reported serial changes in the epidural space after an epidural blood patch. Over a period of 3 mo, clot organization, then collagen deposition, followed by fibroblastic activity and finally shrinkage of collagen layer occurred. Rainbird and Pfitzner (8) suggested that fibrous organization of an epidural blood clot could lead to formation of a barrier in the epidural space that could impede the spread of local anesthetic solution.

Another possibility is that parturients who had dural puncture had abnormal epidural spaces or spinal canals that led to dural puncture initially and impaired spread of local anesthetics subsequently. But, only one of the 46 women with dural puncture had poor epidural analgesia the first time. None of these 46 parturients had a dural puncture during the subsequent insertion of an epidural catheter. An abnormal epidural space would not seem to be a common factor in these 46 parturients.

Patients with post dural puncture headache should not be denied the benefits of epidural blood patch due to concerns about impairment of subsequent regional anesthesia. Although the retrospective nature of this review precludes any cause and effect conclusion, the data demonstrated a significant association between a previous dural puncture and impaired subsequent epidural analgesia. The data also suggest that epidural blood patch, by itself, does not increase the risk of poor analgesia in subsequent epidural anesthetics. A controlled prospective trial with greater numbers would be needed to identify any extra adverse effect due to epidural blood patch on subsequent epidural anesthetics.

Clinically, parturients who request epidural analgesia and who have had previous dural puncture with or without epidural blood patch should be informed that they have a 35%–40% chance of poor analgesia.

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A New Local Anesthetic, Ropivacaine

Its Epidural Effects in Humans

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CONCEPCION M, ARTHUR GR, STEELE SM, BADER AM, COVINO BG. A new local anesthetic, ropivacaine: its epidural effects in humans. Anesth Analg 1990;70:80–5.

The current study was initiated to evaluate the epidural anesthetic properties of 0.5%, 0.75%, and 1.0% ropivacaine, a new local anesthetic agent structurally similar to bupivacaine. Fifteen patients scheduled for lower limb orthopedic surgery were enrolled in the study. As the concentration of ropivacaine increased from 0.5% to 1.0%, the time to onset of sensory anesthesia decreased from 6.4 ± 1.7 (SD) min to 2.4 ± 0.6 min and the maximum level of sensory anesthesia increased from T_6 to T_1. These changes were not statistically significant. Time to regression of anesthesia to T_{12} increased from 255 ± 73 min with the 0.5% solution to 356 ± 75 min with 1.0% ropivacaine ($P < 0.05$). The degree of motor blockade using the Bromage scale varied with the concentration. When the 0.5% concentration was used, only one patient (20%) had greater than 1+ motor blockade. However, all of the patients receiving the 0.75% or 1.0% solution had at least 2+ motor blockade.

Sensory anesthesia was adequate for surgery in 14 of the 15 patients. The mean peak plasma concentration of ropivacaine (C_{max}) increased from 0.65 ± 0.15 μg/mL with the 100-mg dose to 1.30 ± 0.43 μg/mL with the 200-mg dose. No adverse effects were noted in any patient in the study. These initial studies in humans suggest that ropivacaine provides satisfactory sensory anesthesia with minimal motor blockade at a concentration of 0.5%. An increase in concentration resulted in a more profound motor blockade. The C_{max} of ropivacaine in this study was below levels associated with toxicity in animal studies.

Key Words: ANESTHETICS, LOCAL—ropivacaine. ANESTHETIC TECHNIQUES, EPIDURAL—ropivacaine. PHARMACOKINETICS, ROPIVACAINE.

Ropivacaine is a new amino-amide local anesthetic similar in structure to both bupivacaine and mepivacaine (1). Ropivacaine is prepared as the s-isomer rather than a racemic mixture such as bupivacaine. Previous studies involving the isomers of local anesthetics suggest that the systemic toxicity of the s-isomer of various compounds may be less than that of racemic preparations (2,3). Pharmacologic studies in intact animals indicate that ropivacaine possesses an anesthetic profile similar to that of bupivacaine (1,4). Moreover, animal studies have also shown this agent to be less cardiotoxic than bupivacaine (5,6).

Based on the results of animal studies it appeared warranted to conduct human studies to determine the clinical effects of ropivacaine. The current investigation provides preliminary information concerning the clinical efficacy and safety of ropivacaine when employed for epidural anesthesia in humans.

Methods

The current study was conducted as an open label investigation as it represented the initial evaluation of a new drug in humans. The anesthetic properties of 0.5%, 0.75%, and 1.0% ropivacaine administered epidurally were studied in ASA physical status I and II patients undergoing orthopedic surgical procedures of the lower extremities.

The study was approved by the Human Research Committee of the Brigham and Women's Hospital and informed written consent was obtained from all participants in the study. The subjects consisted of 12 men and three women aged 22–60 yr. Medical histo-

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ries and physical examinations were obtained in all subjects before admission into the study. All patients were premedicated with 5–10 mg of oral diazepam approximately 1 h before the induction of epidural anesthesia, or with 1–3 mg of midazolam intravenously immediately before induction. A 14-gauge intravenous (IV) catheter was inserted at the antecubital fossa and 500 mL of lactated Ringer's solution was infused before induction of anesthesia.

Arterial blood pressure, heart rate, and lead II electrocardiogram tracings were taken before induction. The epidural blockade was performed with the patient in the lateral decubitus position. An 18-gauge Tuohy needle was inserted into the epidural space at the $L_{3\text{-}4}$ level using a loss of resistance technique. After identification of the epidural space, a 3-mL test dose of ropivacaine was injected. As an open label study, the first five patients received the 0.5% concentration, the next five patients received 0.75% ropivacaine, and the final five patients received the 1.0% solution. Four minutes after the initial test dose, 17 mL of the designated concentration was then administered through the needle for a total of 20 mL of 0.5% (100 mg), 0.75% (150 mg), or 1.0% (200 mg). Five patients were studied at each concentration. Patients were then immediately placed in the supine position.

The dermatomal level of sensory anesthesia to pinprick was measured at 2-min intervals for the first 30 min after injection of the drug. Thereafter, the sensory level of anesthesia was evaluated at 15-min intervals until complete regression of anesthesia occurred. Motor blockade was assessed using the 0–3+ Bromage scale (7) at the same intervals as sensory blockade until the beginning of surgery. After surgery was completed, motor blockade was determined every 15 min until complete recovery of motor function. Incremental doses of 0.5 mg of midazolam IV were used for intraoperative sedation if necessary.

Adequacy of surgical anesthesia was determined on the basis of the patient's subjective response to surgery and the requirements for supplemental medication to maintain the patient pain-free. If pain or discomfort at the site of surgery was present, IV narcotics and/or general anesthesia were used.

Blood pressure and heart rate were recorded with an automatic blood pressure unit (Dinamap) at 2-min intervals for 30 min after epidural blockade and 5-min intervals thereafter. Electrocardiogram was continuously recorded until the end of surgery. Venous blood samples were drawn from an antecubital vein before the epidural block and at 5, 10, 15, 20, 25, 30, 45, 60, and 90 min and at 2, 3, 4, 6, 9, and 12 h after the epidural administration of ropivacaine. Part of the whole blood sample was retained for analysis and the remainder was centrifuged to obtain plasma. Samples were stored at −20°C until analyzed for ropivacaine concentrations in both whole blood and plasma by a gas chromatographic technique similar to that previously described by Tucker (8). The coefficient of variation of the assay ranged from 11% at 0.05 μg/mL to 3% at 1.0 μg/mL during the course of the study. Concentrations have been expressed as micrograms of ropivacaine HCl per milliliter of fluid. Plasma concentrations were determined so that data could be compared with the study performed by Burm et al. (9) who reported bupivacaine pharmacokinetics after epidural anesthesia based on plasma concentrations. Whole blood concentrations were determined to compare ropivacaine epidural pharmacokinetics with IV pharmacokinetics, which have to date been reported only in whole blood (10). In the interests of clarity, only the plasma concentration and pharmacokinetic data will be fully reported.

Pharmacokinetic analysis was undertaken using the noncompartmental approach described by Tucker (11). A computer program (SIMPLEX) was also used to generate pharmacokinetic parameters based on a one-compartment open model. The program utilizes an opportunistic nonlinear regression technique based on the algorithm of Nelder and Mead (12). The data obtained from these two pharmacokinetic approaches were very similar. Therefore, data presented in the text are those obtained by noncompartmental analysis. The following pharmacokinetic parameters were evaluated: peak whole blood and plasma concentrations (C_{max}), time to peak (t_{max}), apparent elimination half-life ($t_{½,z}$), clearance (Cl), and mean body residence time. Due to difficulty in obtaining a sufficient number of samples from one patient in the 1.0% group, mean data for this group are based on four subjects only.

Statistical analysis of the anesthetic data of ropivacaine was carried out by analysis of variance for linear trends. Linear regression analysis was used to compare dose of ropivacaine with resulting plasma concentrations. Results are expressed as mean ± standard deviation (SD). A *P* value of <0.05 was considered statistically significant.

Results

The demographics of the three groups are shown in Table 1. No statistically significant differences existed between the groups with regard to age or height. The weight of patients receiving 1.0% ropivacaine was significantly greater than that of patients given the 0.5% solution. The surgical procedures performed are

Table 1. Demographic Data

Ropivacaine concentration (%)	n	Age (yr)	Weight (kg)	Height (cm)	Sex (F/M)
0.5	5	42 ± 15	71.2 ± 5.9	166 ± 13	2/3
0.75	5	35 ± 14	77.4 ± 7.0	170 ± 15	1/4
1.0	5	30 ± 17	87.4 ± 12.2[a]	174 ± 11	0/5

Values are mean ± SD.
[a] $P < 0.05$, 1.0% compared to 0.5%.

shown in Table 2. Onset of sensory anesthesia to the T_{12} dermatomal level occurred in 6.6 ± 1.7 min in patients given the 0.5% solution, 6.4 ± 2.5 min in those given 0.75% ropivacaine, and 2.4 ± 0.6 min in those given 1.0% ropivacaine. Although the mean onset time to T_{12} was shorter with the 1.0% solution, this difference was not statistically significant compared with onset times with the 0.5% or 0.75% solutions.

The maximum level of sensory anesthesia increased in a concentration-related fashion. The highest mean level for the three different concentrations was as follows: 0.5%:T_6 (range T_{10}–T_2), 0.75%:T_3 (T_{10}–C_2), and 1.0%:T_1 (T_4–C_2). The differences between the groups were not statistically significant. The time required to reach the highest level of sensory anesthesia was >30 min in each of the three groups (Figure 1).

Times for two-segment regression were essentially the same for the three concentrations studied. However, duration of anesthesia at the T_{12} dermatomal level and total duration of sensory block increased in a concentration-dependent fashion. Duration of anesthesia at T_{12} was 255 ± 73 min for 0.5% ropivacaine, 298 ± 47 min for 0.75% ropivacaine, and 356 ± 75 min for the 1.0% ropivacaine solution. The difference between the 0.5% and 1.0% solutions was statistically significant. There was no significant difference in the total duration of anesthesia between the three concentrations (Table 3).

The degree of motor blockade varied with the concentration used. Patients given 0.5% ropivacaine had minimal motor blockade. Two patients (40%) had 1+ motor blockade, and only one patient reached 2+ motor blockade. With 0.75% concentrations, three patients had a 2+ blockade and three patients had a 3+ degree of blockade. Finally, all (100%) patients receiving 1.0% ropivacaine reached 2+ blockade. The time required to achieve the maximum degree of motor blockade was similar for all the concentrations and occurred within 25 min. No significant difference in the duration of motor blockade existed between the 0.75% solution (345 ± 220 min) and the 1.0% solution (306 ± 100 min). The 0.5% solution resulted in a duration of 1+ motor blockade of 185 ± 77 min. One patient in the 0.75% group had prolonged motor weakness in the L_5-$S_{1\text{-}2}$ roots distribution, which resolved completely within 12–18 h. This explains the longer duration of motor blockade in the 0.75% group.

The quality of anesthesia was judged to be unsatisfactory for the surgical procedure performed in one of the 15 patients. In this patient the 0.75% solution was employed, and significant amounts of IV opioids were required to provide adequate surgical anesthesia. General anesthesia was induced in one patient in the 0.5% group. This was not due to inadequate anesthesia but was requested by the patient as the surgical procedure was longer than anticipated.

Mean arterial pressure after induction of epidural anesthesia gradually decreased below control levels (Figure 2). This decrease in mean arterial pressure was statistically significant only at 10 min with the 1.0% solution and at 25 min with the 0.5% ropivacaine. Changes in mean arterial pressure were not, however, statistically significantly different in the three groups. Changes in heart rate also were not significant. There were no significant changes in the intraoperative or postoperative electrocardiogram.

Plasma concentrations of ropivacaine as a function of time are shown in Figure 3. C_{max} (plasma) increased in a statistically significant dose-dependent fashion, from 0.65 ± 0.15 μg/mL after a dose of 100 mg of ropivacaine to 1.23 ± 0.42 μg/mL after 150 mg of ropivacaine, and 1.30 ± 0.43 μg/mL when 200 mg of ropivacaine was employed ($P < 0.05$). A range of 10–60 min was seen for t_{max}, with the value of t_{max} of 17 ± 8 min with 0.75% ropivacaine being significantly less than the value of 44 ± 14 min with 1.0% ropivacaine. Mean values for the various pharmacokinetic parameters (based on plasma concentration data) are presented in Table 4. The mean elimination half-life ranged from 271 ± 114 min (0.75%) to 748 ± 925 min (1.0%), whereas the calculated clearance of ropivacaine varied from 0.28 ± 0.08 L/min (0.5%) to 0.43 ± 0.10 L/min (0.75%). The apparently longer $t_{½,z}$ value in the 1.0% ropivacaine group was due to one patient having a value of 2207 min. This patient also had the lowest clearance value in this study (0.09 L/min). By comparison, clearance values based on whole blood concentrations ranged from 0.45 ± 0.12 L/min (0.5%) to 0.61 ± 0.09 L/min (0.75%) and C_{max} (blood) increased from 0.43 ± 0.06 μg/mL (0.5%) to 0.83 ± 0.28 μg/mL (0.75%) and 0.95 ± 0.22 μg/mL (1.0%). Blood concentrations are less than plasma concentrations because of plasma protein binding of local anesthetic and the relatively limited uptake of drug into red blood cells. Because blood concentrations are lower than plasma concentrations, the resulting areas under the drug concentration versus time curves (AUC)

Table 2. Surgical Procedures and Duration of Surgery

0.5% Ropivacaine Mean duration, 80 min Range, 42–112 min	0.75% Ropivacaine Mean duration, 121 min Range, 59–246 min	1.0% Ropivacaine Mean duration, 159 min Range, 100–230 min
Removal of screw plate (R) hip	Arthroscopic reconstruction ACL	Knee arthroscopy
	Patella tendon graft	Arthrotomy ACL repair
Knee arthroscopy and debridement	Intramedullary rodding femoral fracture	ACL repair
Repair Achilles tendon	Open reduction of acetabular fracture	Valgus extension osteotomy
Talonavicular and subtalar fusion with iliac crest graft	(R) High tibial osteotomy	Total knee replacement
	(L) Knee arthroscopy	Toe arthroplasty
Removal of Dahl clamp hip	Removal of plate from hip	Excision patella fragment
		Patella repair

ACL, anterior cruciate ligament; L, left; R, right.

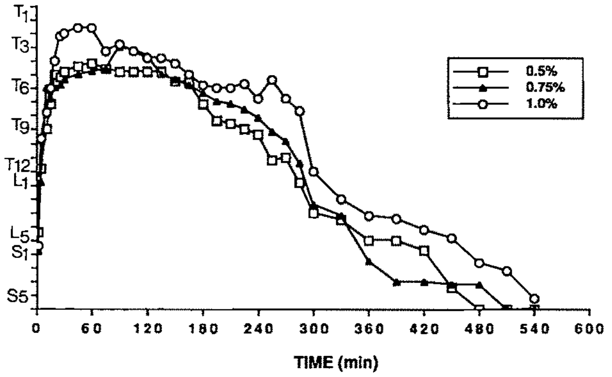

Figure 1. Levels of sensory epidural anesthesia as a function of time with three different concentrations of ropivacaine (n = 5 all groups).

are proportionately different, resulting in higher clearance values (Cl = dose ÷ AUC).

Discussion

Laboratory investigations continue in an attempt to develop new anesthetic drugs with improved efficacy and a greater degree of safety. The local anesthetic drugs currently available offer a varied degree of efficacy, from drugs of low potency such as procaine to drugs eight to ten times as potent such as etidocaine and bupivacaine. Unfortunately, as the potency of local anesthetics increases so does their toxicity. Bupivacaine, one of the most widely utilized local anesthetics, has been the subject of intense investigation because of reports of sudden cardiovascular collapse in some patients (13,14).

Ropivacaine (LEA-103) is a new amino-amide local anesthetic agent similar in structure to bupivacaine. Pharmocologic studies in isolated nerves (15) and intact animals (1,4) have indicated that ropivacaine possesses an anesthetic profile similar to that of bupivacaine but with less potential for cardiotoxicity than bupivacaine (5,6).

The preliminary human studies presented here indicate that ropivacaine in the concentrations studied provides satisfactory anesthesia with minimal blockade of motor function at a concentration of 0.5%. This should be an asset in obstetrical analgesia and anesthesia where prolonged sensory analgesia with minimal blockade is desirable. An increase in concentration resulted in a more profound motor blockade. No adverse effects were encountered with any of the concentrations employed.

Although few statistically significant differences existed between the concentrations of epidural ropivacaine employed in this study, this may have been related to the small number of patients in each group. A tendency did exist for a decrease in onset time, an increase in duration of sensory anesthesia, and a more profound degree of motor blockade as the concentration increased from 0.5% to 1.0%. The maximum dose of 200 mg of ropivacaine administered epidurally in this study was not associated with any symptoms of systemic toxicity. The average peak venous plasma concentration of 1.30 μg/mL achieved after the epidural injection of 200 mg of ropivacaine should be safe. It has been previously reported that venous plasma concentrations of >4 μg/mL of ropivacaine were required for the development of seizure activity in dogs (5).

A comparison of ropivacaine and bupivacaine for epidural anesthesia in dogs showed that the agents had a similar pharmacokinetic profile (16). When comparing data from the current study with those previously reported for epidural administration of bupivacaine in humans (9), a similar pharmacokinetic profile for the two drugs is also apparent under clinical conditions. For example, after the epidural injection of 115 mg of bupivacaine (0.5%) Burm et al. (9) reported that plasma C_{max} was 0.75 μg/mL and t_{max} was 19 min compared with a C_{max} value of 0.65 μg/mL and t_{max} of 24 min after 100 mg of ropivacaine (0.5%) in the present study. The long elimination

Table 3. Sensory Anesthesia After Epidural Administration of Ropivacaine

Ropivacaine concentration (%)	Time of onset to T_{12} (min)	Maximum cephalad level (mean range)	Time to two-segment regression (min)	Time to regression to T_{12} (min)	Time to complete regression (min)	Adequate operative anesthesia (%)
0.5	6.6 ± 1.7	T_6 (T_{10}–T_2)	165 ± 25	255 ± 73	378 ± 38	100
0.75	6.4 ± 2.5	T_3 (T_{10}–C_2)	164 ± 22	298 ± 77	396 ± 34	80
1.0	2.4 ± 0.6	T_1 (T_4–C_2)	157 ± 25	356 ± 75[a]	438 ± 52	100

Values are mean ± SD.
[a] $P < 0.05$, 1% compared to 0.5%.

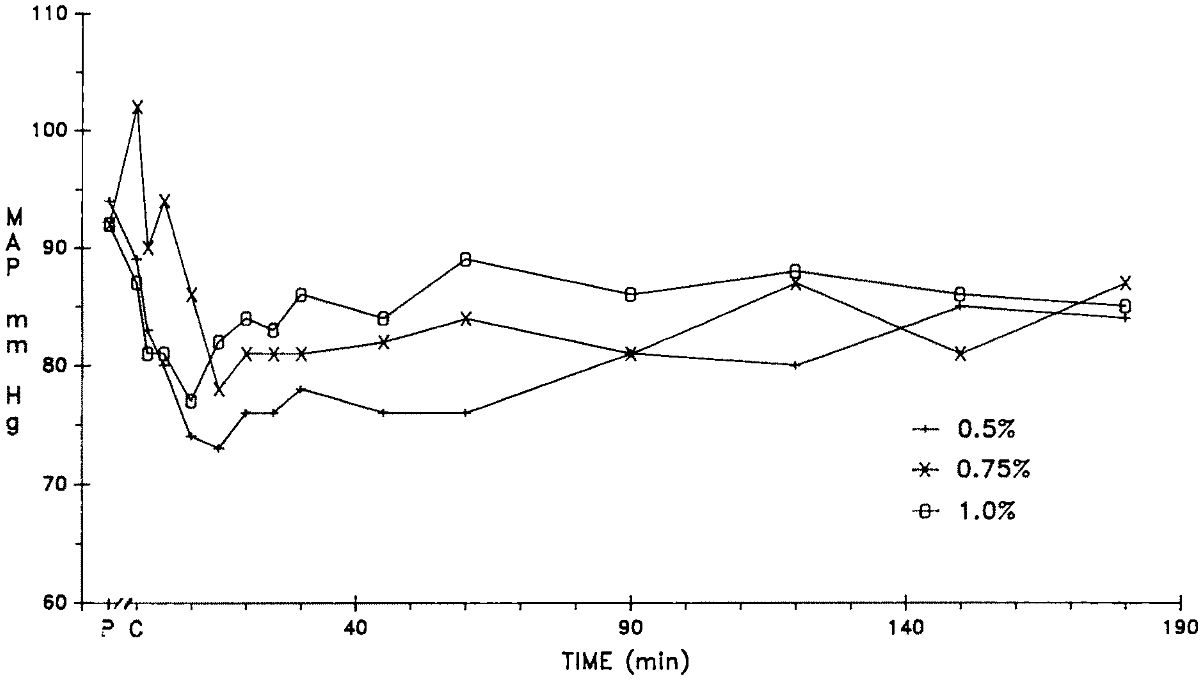

Figure 2. Mean arterial pressure (MAP) before and for 3 h after epidural anesthesia with three concentrations of ropivacaine. P, mean data at the time of premedication; c, mean data before epidural blockade (n = 5 all groups).

half-life and mean body residence time for ropivacaine indicate a relatively slow absorption of drug from the epidural space. This may be due in part to the intrinsic vasoconstrictive properties and high lipid solubility of ropivacaine (17).

The mean value for clearance of ropivacaine determined from whole blood concentrations varied from 0.45 ± 0.12 to 0.61 ± 0.09 L/min, which is somewhat less than that reported after IV infusions in humans (0.73 L/min) (10). This lower clearance after epidural administration of ropivacaine, compared to IV data, has also been reported in dogs (16). Thus, the clearance of ropivacaine after epidural administration is similar to that reported in humans for bupivacaine after IV infusion (0.58 L/min) (18).

A comparison of the anesthetic profile obtained with ropivacaine in this study and previous data reported for bupivacaine (19) suggests that these agents may possess similar anesthetic properties after epidural administration. Both agents provide satisfactory surgical anesthesia with a long duration of action. In addition, both agents demonstrate a distinct separation of sensory and motor fiber blockade when employed as dilute solutions. Increases in concentration of both agents result in a more profound degree of motor blockade.

It is impossible to determine from this study whether ropivacaine is less toxic in terms of the cardiovascular system than bupivacaine. Previous studies in animals suggest, however, that the cardiac toxicity of bupivacaine may be greater than that of ropivacaine when employed in equal doses (5,6). The results of the current study in humans and previous studies in animals suggest that ropivacaine may pos-

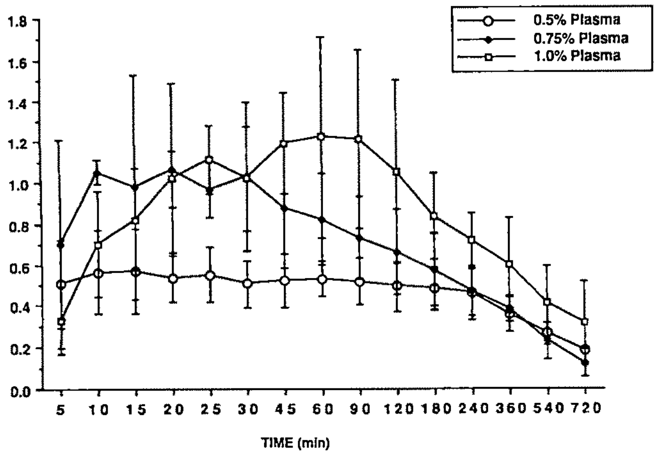

Figure 3. Ropivacaine concentrations in plasma as a function of time after epidural injection ($n = 5$ for 0.5% and 0.75% plasma; $n = 4$ for 1.0% plasma). Data points are mean concentrations ± SD. The *solid line* represents computer-predicted concentrations based on a one-compartment model.

Table 4. Pharmacokinetic Data Derived from Analysis of Plasma Ropivacaine Concentrations

Concentration (%) *n*	0.5 5	0.75 5	1.0 4
Dose (mg)	100	150	200
Cl (L/min)	0.28 ± 0.08	0.43 ± 0.10	0.31 ± 0.19
$t_{1/2,z}$ (min)	422 ± 68	271 ± 114	748 ± 975
MBRT (min)	604 ± 87	381 ± 156	924 ± 1086
C_{max} (μg/mL)[a]	0.65 ± 0.15	1.23 ± 0.42	1.30 ± 0.43
t_{max} (min)	24 ± 21	17 ± 8	44 ± 14[a]

Cl, total body clearance; $t_{1/2,z}$, apparent elimination half-life; MBRT, mean body residence time; C_{max}, peak plasma concentration; t_{max}, time of occurrence of C_{max}.

[a] $P < 0.05$, 1.0% compared to 0.75%.

sess an anesthetic profile similar to bupivacaine with the advantage of an enhanced therapeutic index. Clearly, further studies that directly compare these two agents in humans are warranted.

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Neuromuscular and Cardiovascular Effects of High-Dose Vecuronium

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TULLOCK WC, DIANA P, COOK DR, WILKS DH, BRANDOM BW, STILLER RL, BEACH CA. Neuromuscular and cardiovascular effects of high-dose vecuronium. Anesth Analg 1990;70:86–90.

The effects of bolus administration of large doses of vecuronium on the onset and duration of neuromuscular blockade and histamine release were studied during fentanyl-nitrous oxide anesthesia. Forty adults were randomly assigned to receive a bolus injection of either 0.1, 0.2, 0.3, or 0.4 mg/kg of vecuronium. The evoked electromyogram of thumb adduction to train-of-four stimulation was monitored. The time of onset and clinical duration (mean ± SEM) after each dose were as follows: 0.1 mg/kg, 164 ± 27 s and 42 ± 5 min; 0.2 mg/kg, 120 ± 17 s and 68 ± 8 min; 0.3 mg/kg, 88 ± 17 s and 111 ± 19 min; 0.4 mg/kg, 78 ± 19 s and 115 ± 19 min. Both time of onset and duration after doses of 0.3 or 0.4 mg/kg were significantly different from values after the lower doses. No dose-related changes in blood pressure, heart rate, or histamine release were observed. The authors conclude that large bolus doses of vecuronium can be safely used to speed the onset of blockade, but with a significantly prolonged duration of action.

Key Words: NEUROMUSCULAR RELAXANTS, VECURONIUM.

Vecuronium has become one of our most frequently used nondepolarizing muscle relaxants because it has a relatively short duration of action, minimal cardiovascular effects, and an apparent lack of histamine-releasing properties (1,2). The absence of cardiovascular effects has led investigators to propose using a large dose of vecuronium to achieve another desired goal—a shorter onset of action (3–5). Therefore, we set out to determine the effects of bolus administration of larger doses of vecuronium, up to 0.4 mg/kg, on the onset and duration of neuromuscular blockade, histamine release, heart rate, and blood pressure.

Patients and Methods

Forty adult patients (ASA physical status I, II, or III) undergoing low-risk surgical procedures of at least 2-h expected duration were studied. The study was approved by the Protection of Human Subjects Committee of Montefiore Hospital, and written informed consent was obtained from each patient. Patients with known disorders of the renal or hepatic system, marked obesity, or neuromuscular disease were excluded. No patient received aminoglycoside antibiotics, antihistamines, or narcotics within the 48 h preceding the study. No premedication was administered. Each patient was randomly assigned to one of four groups ($n = 10$ per group) to receive a single dose of either 0.1, 0.2, 0.3, or 0.4 mg/kg of vecuronium bromide.

Anesthesia was induced with thiopental (mean dose, 5.7 mg/kg), midazolam (mean dose, 0.03 mg/kg), and fentanyl (mean dose, 4.2 μg/kg). Anesthesia was maintained with nitrous oxide (60%–70% inspired) and additional thiopental (mean dose, 1.8 mg/kg), midazolam (mean dose, 0.025 mg/kg), and fentanyl (mean dose, 5.5 μg/kg) using clinical criteria. Ventilation was controlled to maintain an end-tidal carbon dioxide concentration of 30–40 torr as measured by mass spectroscopy. Esophageal temperature was monitored and maintained within 1.0°C of the baseline value.

After the induction of general anesthesia, the ulnar

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nerve was stimulated supramaximally with repetitive trains-of-four (2 Hz for 2 s at 20-s intervals) using surface electrodes. The evoked compound electromyogram of thumb adduction was recorded using a Puritan-Bennett/Datex monitor. Electromyographic monitoring continued for 3 min to establish a stable baseline before the administration of vecuronium. The degree of neuromuscular blockade was characterized as the ratio of the height of the first response (T_1) of the train-of-four to the height of the control electromyogram (T_c).

Vecuronium was administered into a rapid intravenous infusion through a T-port located at the catheter. The time from injection to the peak reduction of the electromyographic signal was taken as the onset time. At this point, the trachea was intubated by an experienced anesthetist and the conditions were scored using the following criteria:

Excellent: jaw relaxed; vocal cords apart and immobile; no diaphragmatic movement
Good: jaw relaxed; vocal cords apart and immobile; some diaphragmatic movement
Poor: jaw relaxed; vocal cords moving; "bucking"
Inadequate: jaw not relaxed; vocal cords closed

Measurements of pulse and blood pressure were made with an automated noninvasive measurement device (Dinamap) at 1-min intervals. Venous blood was collected for measurement of histamine levels immediately before administration of vecuronium and at 1, 3, and 5 min after vecuronium was given. Blood samples were immediately placed in a high-speed centrifuge to separate the plasma, which was then frozen in liquid nitrogen. Plasma histamine levels were determined radioimmunologically using the competition for binding of acylated histamine and ^{125}I-labeled acylated histamine to mouse monoclonal antibody. This assay is linear between 100 and 5000 pg/mL with excellent reproducibility and is sensitive to 100 pg/mL (6).

Neuromuscular function was allowed to recover spontaneously to 25% of baseline. If additional relaxation was required by clinical circumstances, vecuronium was administered in 0.025-mg/kg increments. The interval between injection and return of the first twitch (T_1) to 25% of control was recorded as the clinical duration of neuromuscular blockade. At the conclusion of surgery, the residual blockade was antagonized with edrophonium (1 mg/kg) and atropine (7 μg/kg). Neuromuscular recovery was referenced to final electromyographic baseline when the response to the train-of-four was stable and T_4/T_1 was >0.9.

Table 1. Onset and Duration of Action by Vecuronium Dose

Dose (mg/kg)	*n*	Onset (s)	*n*	Duration (min)
0.1	10	164 ± 27 (60–360)	10	42 ± 5 (25–69)
0.2	10	120 ± 16 (100–140)	7	68 ± 8 (50–106)
0.3	10	88 ± 17[a] (60–120)	8	111 ± 19[a] (62–208)
0.4	9	78 ± 19[a] (60–100)	7	115 ± 19[a] (35–191)

Mean ± SEM (range).
[a] Significant difference compared with doses of 0.1 and 0.2 mg/kg.

The differences between groups were assessed by analysis of variance and the Student–Newman–Keuls multiple range test. Cardiovascular and histamine data were assessed using repeated measures analysis of variance. Differences were considered significant at $P \leq 0.05$.

Results

The patients' ages ranged from 18 to 59 yr with a mean of 38 yr. The mean body surface area was 1.8 m^2. There was no significant difference among the groups with respect to age or body surface area.

The time to onset decreased as the dose increased (Table 1). The reduction was statistically significant between doses of 0.2 mg/kg and both 0.3 and 0.4 mg/kg; however, there was no significant difference between doses of 0.1 and 0.2 mg/kg or 0.3 and 0.4 mg/kg (Figure 1, Table 1).

All patients were intubated when neuromuscular function of the adductor pollicis was completely blocked. One patient who received 0.3 mg/kg of vecuronium developed mild diaphragmatic movements 150 s after vecuronium administration. In all others, intubation conditions were excellent.

The clinical duration of paralysis was increased with increasing dose (Table 1). Duration was statistically significantly increased between doses of 0.2 mg/kg and both 0.3 and 0.4 mg/kg; however, there was no significant difference between doses of 0.1 and 0.2 mg/kg or 0.3 and 0.4 mg/kg (Figure 2). Data on complete spontaneous recovery were obtained only in ten patients because completion of surgery and anesthesia precluded continued monitoring.

Thirty patients were given edrophonium for antagonism of residual blockade at the completion of the operation. There was no significant difference in either the residual blockade or the time-course of recovery among the groups. The residual blockade

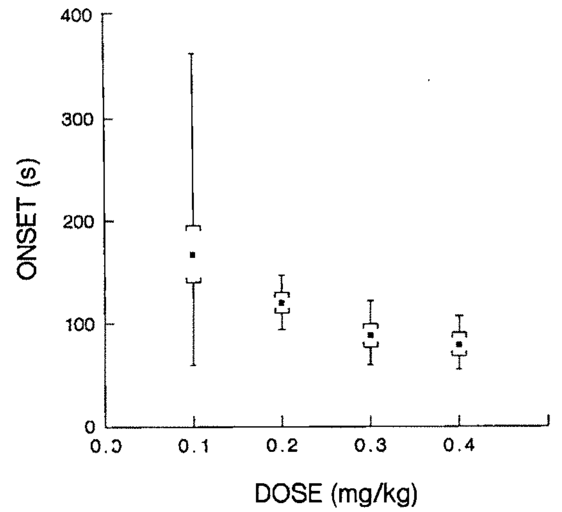

Figure 1. Effects of dose of vecuronium on time to onset of complete blockade (mean ± SEM and range). The onset times with doses of 0.3 and 0.4 mg/kg are significantly different from those with lower doses.

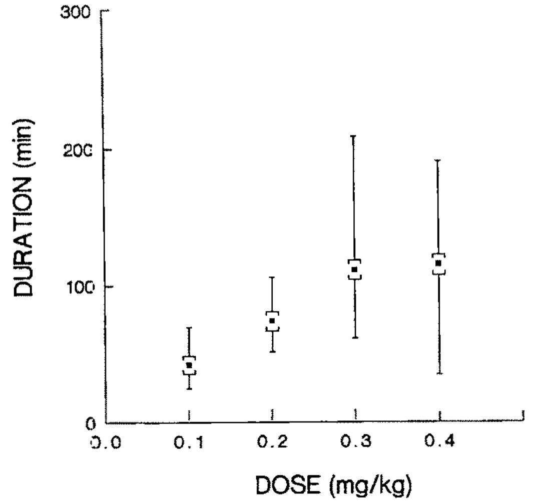

Figure 2. Effects of dose of vecuronium on clinical duration (mean ± SEM and range). The clinical duration with doses of 0.3 and 0.4 mg/kg are significantly different from that with lower doses.

(T_1) before edrophonium averaged 50% of baseline. Two minutes after edrophonium was given, neuromuscular transmission had recovered to 84% of baseline, and by 5 min it had recovered to 90% of baseline in the average patient. Provided that spontaneous recovery had occurred to a T_1 of >30% of control, edrophonium antagonized the residual blockade within 5 min to a T_4/T_1 ≥70% (Figure 3). Two patients with complete blockade were given edrophonium 31 and 138 min after 0.4 mg/kg of vecuronium. Maximal recovery to 58% and 93% of baseline, respectively, was achieved by 5 min.

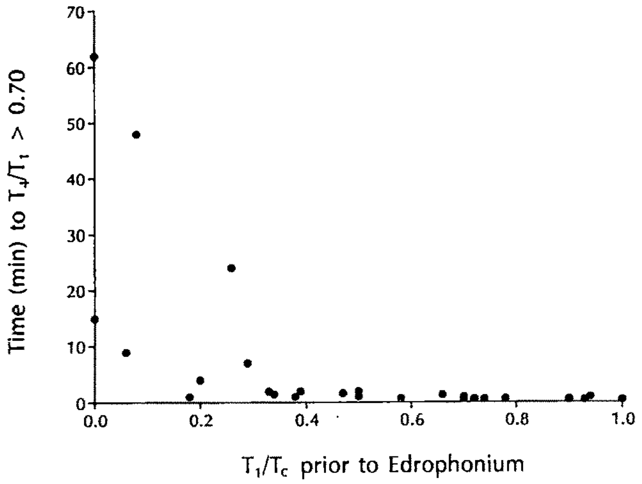

Figure 3. Times required to achieve a T_4/T_1 ratio of >0.7 as a function of T_1/T_c at the time of edrophonium administration. Rapid antagonism of the residual blockade occurred provided that T_1/T_c was >0.3.

Mean blood pressure and heart rate data are presented in Table 2. There was no evidence of a dose-related change in blood pressure or pulse. There was a statistically significant decrease in blood pressure, however, at 1 min after vecuronium administration in all groups. The mean blood pressure decreased by an average of 7 mm Hg.

One hundred and fifty plasma samples were obtained for histamine analysis. The mean values for all groups and measurement intervals fell within the normal range of <1000 pg/mL (Table 3). There were no significant differences in plasma levels related to doses of vecuronium given. No patient had bronchospasm, flushing, or hives.

Discussion

Vecuronium has proved to be a cardiovascularly stable nondepolarizing relaxant of intermediate duration when used in doses of <0.08–0.1 mg/kg (7). Several of the older relaxants cause histamine release in clinical doses, as does atracurium, the other currently available relaxant of intermediate duration (8). This study examines what benefit accrues from increasing the bolus dose of vecuronium, in terms of onset time, and at what cost in cardiovascular stability, histamine release, and duration of action.

Increasing the bolus dose of pancuronium or atracurium can modestly shorten the onset of action, but this strategy has limited clinical utility because of the undesirable cardiovascular consequences (1,8,9). Previous studies with vecuronium have demonstrated significant reductions in onset time as the dose was

Table 2. Heart Rate and Mean Arterial Pressure

Dose (mg/kg)	Control		1 min after relaxant		3 min after relaxant		5 min after relaxant	
	HR	MAP	HR	MAP	HR	MAP	HR	MAP
0.1	65 ± 3	81 ± 3	64 ± 3	75 ± 3[a]	72 ± 5	85 ± 5	65 ± 4	84 ± 4
0.2	66 ± 3	83 ± 4	66 ± 4	77 ± 5[a]	69 ± 5	89 ± 5	65 ± 3	83 ± 4
0.3	65 ± 3	85 ± 4	62 ± 3	72 ± 4[a]	66 ± 4	83 ± 8	66 ± 5	80 ± 5
0.4	76 ± 4	81 ± 3	70 ± 3	78 ± 4[a]	78 ± 4	94 ± 5	75 ± 4	91 ± 4

HR, heart rate (beats/min); MAP, mean arterial pressure (mm Hg).
Values are mean ± SEM.
[a]Significant difference from control.

Table 3. Plasma Histamine Concentration

Dose (mg/kg)	Control	1 min after relaxant	3 min after relaxant	5 min after relaxant
0.1	475 ± 91 (210–1079)	518 ± 91 (209–1169)	346 ± 65 (50–682)	524 ± 109 (50–1076)
0.2	372 ± 78 (83–703)	478 ± 105 (50–897)	519 ± 126 (157–1270)	687 ± 244 (106–2390)
0.3	616 ± 111 (87–1209)	476 ± 98 (127–823)	664 ± 177 (175–1882)	613 ± 200 (103–2321)
0.4	491 ± 140 (60–1308)	405 ± 86 (151–887)	450 ± 128 (50–1508)	840 ± 412 (50–4386)

Values are mean ± SEM (range) in picograms per milliliter. No significant differences between doses.

increased; succinylcholine was not used as a control group in these studies (3,10,11). We demonstrate in this study a general reduction in onset time with increasing dose. The average onset time was reduced to 88 s by increasing the dose from 0.1 to 0.3 mg/kg, and the range in onset time was greatly decreased. Increasing the dose further to 0.4 mg/kg did not produce a significantly faster onset time, suggesting that 0.3 mg/kg might be the optimal dose for the most reliable and rapid onset. Compared with our onset time of 78 s with 0.4 mg/kg, Kaufman et al. (11) observed an onset time of 94 s, and Casson and Jones (10) 44 s. The differences between our data and those of Kaufman et al. are probably not significant. Casson and Jones used a force transducer to measure neuromuscular blockade and also used a shorter interval between train-of-four stimuli (12 s), either of which may have contributed to their shorter onset time (12).

Our study was not designed to determine how quickly intubation can be achieved; however, excellent intubating conditions correlated with 100% blockade in our patients. Thus, with 0.3 mg/kg excellent intubating conditions could be achieved in the average patient at 88 s.

No adverse cardiovascular effects were noted as the dosage increased. The pulse rate showed no significant change within dosage categories after vecuronium was administered or between dosage categories at any time period. Mean arterial pressure showed a statistically significant but clinically insignificant decrease from control measurements to the measurement at 1 min after vecuronium. This decrease was present in all dosage groups and showed no change in magnitude as dosage increased. Thus, the transient decrease in blood pressure is probably unrelated to vecuronium but more likely related to effects of induction of anesthesia and controlled ventilation. Intubation of the trachea was performed between 1 and 3 min, thus the 3- and 5-min measurements reflect the influence of that stimulus.

Although in a few plasma histamine samples histamine level was above the normal range, they were spread through all groups and time periods. There was no consistent or significant increase in histamine level as vecuronium dosage was increased. Thus, our study confirms the findings of Cannon et al. (5) and extends the examination of the histamine-releasing potential of vecuronium to a higher dose. Recently, it has been reported that clinically used doses of vecuronium inhibit histamine *N*-methyl transferase, the enzyme primarily responsible for the metabolism of histamine (13). Although plasma histamine may occasionally be elevated after vecuronium administration, either as a direct effect or by inhibition of histamine *N*-methyl transferase, we could find no clinically significant dose-related effect of vecuronium on heart rate and blood pressure during the 5 min after its administration. Thus, high-dose vecuronium appears to have no added cost in terms of adverse cardiovascular consequences.

Vecuronium at high doses does not have an intermediate duration of action. A dose of 0.3 mg/kg (five times the ED_{95}) required 111 min to recover to 25% of baseline—a clinical duration longer than that of the usual dose of pancuronium. Katz observed that at 0.08 mg/kg (1.5 times the ED_{95}) of pancuronium, the time to recover to 25% of baseline was 86 min (14). Provided that spontaneous recovery had occurred to a T_1 of ≥30%, edrophonium antagonized the residual vecuronium blockade to T_4/T_1 of >70% within 5 min (Figure 3).

In summary, we found that the time to complete neuromuscular blockade can be reduced by almost 50% by increasing the dose of vecuronium from 0.1 to 0.3 mg/kg. Doses up to seven times the ED_{95} are free of clinically significant effects on blood pressure and heart rate. Bolus administration of up to 0.4 mg/kg of vecuronium is not regularly associated with histamine release. The price paid for the shorter onset of 0.3 mg/kg is a clinical duration of action increased to 2.5 times that of 0.1 mg/kg.

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Special Article

A Template for Writing a Scientific Paper

Edmond I. Eger II, MD

Key Words: PUBLICATIONS.
EDUCATION, WRITING.

A template is "a gauge, pattern or mold (as a thin plate or board) used as a guide to the form of a piece being made" (1). For the discussion that follows, I will supply a template that may be used to construct a paper describing research in anesthesia—or any scientific discipline. The template does not indicate the approach that might be taken for other purposes (e.g., writing a review paper). The format follows that used for papers on research (title, authors, abstract, introduction, materials and methods, results, discussion, and figures and tables). The analysis of each topic is limited, and the reader wishing greater detail can refer to texts on the subject such as those by Day (2) and Huth (3).

Title

The title must describe your work in a few words without sacrificing accuracy (well, without sacrificing very much). It is a tease for the reader. A question makes a good title: "Does X Decrease (or Increase or Cause) Y?" An assertion may be even better: "X Decreases Y." Then, if the result is just what the readers expect, they may feel they don't need to read the article! Avoid nonspecific questions or assertions ("Does X Affect [or Change] Y?" "X Changes Y"). Be specific about what you anticipate studying or finding. The title usually also includes the species studied (presuming that a species was studied). "X Increases Y in Rats." This gives the nonrat reader a signal to go on to the next article.

Authorship

Who should be listed as an author, and what determines the order in which the authors should be listed? Conventional wisdom suggests that authors should be those who have made a material contribution to the paper. The problem comes in defining "material." Webster says it is "having real importance or great consequence . . . essential . . . relevant, pertinent" (1). I tend to be more generous (realistic?) and include all those who have contributed in any appreciable way (now define appreciable!). Many would frown on my view and limit authorship to those who provided contributions as defined by Webster. However, I believe that there are certain realities of academe and ego. For example, it is sometimes prudent to include the name of the physician whose patients were used and who, beyond that, participated to the extent of discussion of the project, including, perhaps, the shaping of the protocol and critique of the final manuscript. You may wish to pursue further studies with his or her help (patients) and coauthorship may aid in cementing your relationship. This may seem a bit Machiavellian in some people's eyes, and realistic in others. I am not taken by the argument that it does harm (e.g., by diluting the credit of those who made greater contributions, or by enrolling authors who do not take sufficient responsibility for the integrity of the work).

In days gone past, the head of a department or laboratory might insist that he or she be given senior (first) authorship. My view is that the person who does the most work is the senior author. However, the senior author also must be the primary writer of the paper and relinquishes senior authorship if he or she foregoes that responsibility. Similarly, the position of the succeeding authors should be determined by the magnitude of their contribution. Some weight may be given to the concept contribution (i.e., some investigators would give senior authorship to the person who contributed the basic concept, even if that person did not work as hard as others in testing the concept), but my view is that concept contribution carries but a limited weight.

Two more points might be made about the first and last authors. Some believe that last is second to

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first in "prestige," last often indicating the developer of the concept for the research. The organizer of a multiinstitutional study may take the last position if he or she does not write the paper (first, if he or she does). Finally, remember that reference citations may only include the first three authors, the remaining authors being consigned to the purgatory of "et al."

It is presently assumed that all authors carry a responsibility for the accuracy and content of the final manuscript (3). They are the primary guardians against fraud (unfortunately, a real concern). Thus, one who has not read the final manuscript or who does not agree with or understand what is written, must not be a coauthor. The author must have an "ability to justify intellectually the conclusions of the paper, including [a] defense of the evidence and counterevidence weighed in reaching the conclusions" (3).

Abstract

Some investigators believe that the abstract—indeed, the whole paper—should be written before the study begins. Such an approach forces the investigator to consider the defense of the methods and discussion at a time when modifications can be made at little cost. However, I believe that the abstract should be written after the paper has been completed. Only then will the necessary overview be available. Because most readers will not read the entire article (really, they won't), and because only the title and abstract will be available by computer search, the abstract must convey all the important messages. The abstract is composed of three or four parts, each of which parallel the larger work that follows:

1. The opening should state the question addressed by your work and indicate why the question is important. It is a mini-*introduction* that only great writers can achieve in one sentence (but that's all it should take).
2. Next should follow a statement of how you answered the question (i.e., the *methods*). Do not get carried away here.
3. The crucial *results* are next. Again, do not get carried away. Use one or two data sets to illustrate the important relationships that you found. Avoid vague generalizations.
4. End with the *conclusion of the discussion*. Do **not** end with a platitude ("The implications of these findings will be discussed").

Introduction

The introduction should induce the reader to believe that there is an important controversy or new, previously missing quintessential information that you, the author, are about to resolve or supply. (Remember, however, that by the end of the paper you *do* have to supply that resolution or information.) It should provide the background, the purpose (the question to be answered), the approach to the problem, and sometimes, the answer. The introduction should be short, usually no longer than one to three paragraphs. It often contains the following:

1. The *background* that led you to ask the question. This gives you a chance to indicate the importance of the work.
2. The *question* or *purpose* of the study. This is the crucial element of the introduction. You can begin the introduction with this point (rather than background) or let the background lead to it. One or more of several purposes may have led to the investigation:
   a. To answer a question raised by previous work, your own or that of others. The good experiment leads to yet another or ten others. (This keeps the unemployment rate for scientists at a low level.)
   b. To resolve controversy. Scientist Smith writes that X is true. Scientist Jones writes that it is not. You will contribute the definitive answer. (However, be sure that you can add something that is more than another vote.)
   c. To confirm an important finding, particularly one that is controversial or questionable. This purpose is close to that stated in "b."
   d. To disprove the work of others. This is one of the most delightful of purposes. It gives the author the chance to write (carefully, and with restraint) "you idiot," and all for the sake of science! The purpose occasionally goes beyond enjoyment of the role of critic to the prevention of fraud in science.
   e. To supply new information. There should be a need for the new information. For example, what is the death rate associated with anesthesia? Knowing this would indicate whether a detailed study of the causes of such death would be of value to society. Another example: What is the pharmacology of a new anesthetic? Knowledge of the pharmacology would indicate what the clinician might expect when he or she uses the new agent.

   However, the publication of new material that has no importance can be a bore and sometimes smacks of data dredging: "Let's cross a rutabaga and a peony," said the professor. "You can't do that," observed the king. "I know," replied the professor, "but think of the interesting things we might find along the way." Usually the findings are pretty dull stuff.

3. A glimpse of *how the question might be answered*. You might indicate the experimental design and the species used, but I don't feel strongly about this.
4. Sometimes, but not always, *the answer*. Giving the answer allows the reader to anticipate the data that will be forthcoming. However, it also supplies a bias that may cause the reader to be less critical of the methods and results.

Materials and Methods

The first purpose of this section is to allow the reader to understand what was done and to determine whether it was adequate to answer the question. The second purpose is to allow another researcher to repeat the experiment. The details in the materials and methods section must allow for both purposes.

Under unusual circumstances, the second purpose may not be completely addressed. The specifics may be so detailed that their inclusion would be inappropriate. In such cases, the investigator has several options. First, if the methods, in and of themselves, are of interest, then a separate paper may be constructed. In such a paper, the methods become the results. A "methods" paper is common in some areas of science (e.g., biochemistry), but is uncommon in anesthesia. Second, the reader can be advised to communicate directly with the investigator for details. Third, the details can be placed in an appendix to the paper or in an archival repository (e.g., the American Documentation Institute).

The materials and methods may include four items:

1. The *species* studied. The review and approval of experimentation committees should be noted. The characteristics of the study population should be described, e.g., the number, age, sex, health, species, and vendor of animals: "We used five, 1-wk-old, male, specific-pathogen-free, Sprague–Dawley rats (Charles River Laboratories, Inc., Wilmington, Mass.)." Include the nutritional regimen ("Rats were fed standard rat chow, ad libitum") and environmental conditions ("The animals were housed in hanging wire-basket cages in rooms maintained at 22°–24°C during a 12-h cycle of light and dark"). The composition, source, and purity of chemicals or drugs used may need to be stated. The above examples pertain to a study in animals. A similar example can be given for a clinical study: "We excluded patients younger than 70 yr, obese patients, or those having documented cardiovascular, respiratory, or hepatorenal disease. No subject was taking drugs known to induce hepatic enzymes. Each was brought to the study room after an overnight fast."
2. The *procedures*. These may include the preparation of the animal, the collection and analysis of specimens, and the statistics applied to the data. Samples excluded from analysis must be described and an explanation given for their exclusion. You may wish to defend the methods employed. Such a defense may be related to the methods previously employed by yourself or others (e.g., "We dried the soda lime at 80°C because we found that higher temperatures decreased the capacity of soda lime to absorb anesthetic").
3. The *protocol* or *sequence of steps*. The sequence of steps must follow a logical path. However, do not be bound by the sequence actually used. Describe the protocol in the simplest manner that accurately reflects the thread of the experiment.
4. The *statistical methods* employed.

Include a description of the methods used to obtain control data. Make clear to the reader that the controls were treated in the same manner as the experimental group(s), except for the imposition of the independent variable(s) that distinguished the experimental group(s). (One can argue that it is not necessary to make this statement because such an approach is essential to good science and therefore can be assumed. Not so, unfortunately!) Similarly, clearly state the comparisons made among experimental groups.

Methods should not include portions of the study that were abandoned, unless there is good reason to believe that the information would prevent other investigators from making the same mistake—and that they would otherwise be likely to make that mistake. Sometimes, a study changes emphasis or direction. Sometimes, an approach is determined to be wrong, or the analysis is flawed (we forgot to include/exclude X, Y, or Z). If data are irrelevant, do not include the methods used to acquire the data. However, you must be careful not to discard results simply because they do not agree with your bias, "didn't make sense," or "detracted from the message we wanted to get across." This can be a difficult ethical point!

Once you have arrived at a sequence for the "Methods" section, try to follow that sequence in subsequent sections, particularly the "Results" section. If you describe how you determined MAC for anesthetics X and Y and then proceed to how you used those MAC values to determine the relative respiratory depressant effects of the two anesthetics, do not subsequently (e.g., in the "Results" section) reverse the order of topics (e.g., describe the relative respiratory depressant effects before describing the MAC values obtained).

Results

This section should organize the data gathered in a manner that leads the reader to the conclusions of the paper. However, the investigator must include conflicting as well as supporting data.

The organization should be as simple as possible. Format data for the easiest comparison. Usually figures and/or tables are most effective (see the section below, "Figures and Tables"). Editors generally prefer the data in one, but not both, of these forms (i.e., they avoid duplication). However, I often include both forms because a graphic representation offers a visual comparison that tabular data cannot provide, and a tabular presentation allows statistical comparisons (by other investigators) that a graphic representation cannot provide.

The text should not duplicate or simply point to the figures and tables but should give the general relationships detailed by the tables and figures. Thus, do not write: "The results for the determination of cardiovascular measurements are given in Table 1." Instead, write: "Cardiac output decreased as a function of the concentration of both isoflurane and enflurane (Table 1)." Or: "An increase in anesthetic concentration produced circulatory depression (Table 1, Figures 1–3)." If you use a general opening statement similar to the last example, follow with a description of specific relationships, but do not repeat data already given in tables or figures.

I usually put the levels of statistical significance in the tables or figures and do not repeat them in the "Results" or "Discussion" section. One can write: "Cardiac output decreased significantly as the inspired concentration of anesthetic was increased." However, the use of the word "significantly" is not necessary for two reasons. First, the level of significance is given in the table or figure. Second, if a correlation is stated, significance is assumed (otherwise one cannot write that the correlation exists).

Sometimes data indicate a trend that approaches but does not reach significance. You may wish to point to such a trend. If so, describe the trend and indicate the specific level of significance obtained: "Blood pressure tended to decrease with an increase in the concentration of isoflurane ($P = 0.073$)."

Usually the "Results" section should contain only results. Comments about the results should be reserved for the discussion section. Occasionally, this is not true, particularly if the comment requires only one sentence and can be juxtaposed to the object it addresses.

Discussion

The discussion must contain some elements and may contain others. Vital elements relate to the question posed in the introduction. The discussion should:

1. Explain how the results serve to answer the question that provoked the study: "Fluoride ion concentrations in phenobarbital-, ethanol-, or nonpretreated rats given I-653 were not higher than those in control animals. In contrast, rats pretreated with phenobarbital and given 1.6 MAC isoflurane for 2 h had peak serum levels of inorganic fluoride 7- to 10-fold higher than peak levels in control rats. These findings support our thesis that the substitution of fluorine for chlorine in isoflurane produces a more stable molecule, one that resists degradation both in vitro and, as in the present study, in vivo."
2. Relate the findings to those previously published. (Be fair in crediting previous discoveries. If your findings are the same as those of a previous investigation, note that your findings confirm those from that investigation—and not the other way around.)
3. Emphasize what is new, different, and important about the findings. Place them in a proper perspective, again being careful to credit those who have helped develop the point you now make.
4. Consider alternative explanations. Address the possibility of errors in your methods and the implications of such errors for the results and conclusions.
5. Discuss inconsistencies within your data or between your data and those of others. Resolve conflict, if possible, but allow for unresolved conflict if no explanation is obvious. ("We have no explanation for these disparate results.")

The Discussion may also include:

1. Implications for clinical practice. Beware of extrapolating too far—animals are not humans; results from studies made in anesthetized animals may not apply to awake animals or humans.
2. Implications for future research. Be specific; do not write: "This matter deserves further exploration." A parallel, useless comment is: "This drug deserves further trials." If such an injunction is implied by the data, the data will say it better than you can. If not, your recommendation is foolish.
3. Other speculations. Do speculate, but be restrained in your speculations. Limit speculations to those that require one or, at most, two assumptions. Identify speculations as such.
4. Problems that developed that might alert future investigators to potential pitfalls (e.g., the soda

lime problem noted earlier). Such comments also can be inserted in the "Methods" section.

These suggestions imply an order of presentation. In fact, the order of presentation should take into account what you wish to emphasize, and should be consistent. You usually should place the most important point at the beginning of the discussion. Sometimes you will wish to leave the reader with that thought and place it at the end. If possible, the progression of thoughts should be logical and the connections between thoughts apparent. Do not separate connected thoughts (in either sentences or paragraphs).

Try to make the first sentence in each paragraph give an overview of the contents of the paragraph. This recommendation applies to all sections (indeed, to all good expository writing), but seems to apply with particular force to the "Discussion" section. I have seen many paragraphs strewn with random thoughts, each one bearing little connection to the next.

Figures and Tables

Figures and tables demonstrate relationships and summarize data. Although figures and tables may support the "Methods," "Results," and "Discussion" sections, they are most commonly located in the "Results" section (but also are referred to in the discussion). Figures and tables used in the "Methods" section may illustrate apparatus or a matrix of drug administrations (i.e., an order of presentation of independent variables such as drug administrations). Figures and tables given in the "Results" section convey the data obtained. Figures and tables in the "Discussion" section usually compare the present results with those previously published.

Clarity and simplicity are vital elements of tables and figures. Excessive detail is to be avoided. Figures should show relationships, but cannot do so if too many data points are included. Unimportant data need not be presented in any section (despite the great effort that may have been expended in their acquisition). If a table is too big, break it down into two tables. Alternatively, I have often seen two tables—or more—where one would do. Take advantage of rows or columns that would be common to two or more tables in considering whether to combine such tables.

The data should be presented as accurately as possible. However, this does not mean that the data should be extended to six significant figures if the accuracy of measurement was only to two. More numbers also are distracting to the reader. It is easier to keep 1.2 in mind than 1.21494.

The material presented in figures and tables should be consistent with the text of the paper. This rule seems obvious and yet is sometimes ignored. If one uses the phrase "duration of surgery" in the text, one should not use the phrase "duration of anesthesia," for the same data, in the table.

Each figure and table should stand alone. That is, it should be intelligible with minimal or no reference to the text. Many readers have adopted the despicable habit of looking *only* at the tables and figures. Someone who has read the abstract should be able to understand the tables and figures without reference to the text for methods, results, or discussion. A lengthy title or legend may be required to allow the table or figure to stand alone. Do not use "Data" as a title. An appropriate title might be: "Values for Heart Rate and Blood Pressure Before and After the Induction of Anesthesia with Isoflurane."

Labels in figures must be large enough to tolerate the decrease in size that usually occurs in the transition from glossy print to published page. If several labels are used, the relative size of each should indicate to the reader their relative importance. Some authors supply a legend identifying the several graphs that may appear in a figure (e.g., a square and continuous line = halothane, a circle and a dashed line = isoflurane). I prefer to overlay directly each graph with the appropriate name (e.g., halothane and isoflurane). This decreases the debris and immediately identifies the graph.

Some purists insist on the insertion of the variance for every point on a graph. I prefer to leave that to the tables (another reason for having both figures and tables), particularly if there are many points to be plotted. Inclusion of variance may make a graph too fussy to be effective. I usually include only one limb of the variance in graphs (i.e., either the "+" or the "−"). This approach halves the number of variance lines and bars but does not decrease the information available to the reader.

Many investigators prefer the use of standard deviations rather than standard errors. The latter indicate the likelihood of mean values differing, and I often prefer them for that reason. (My statistical friends accuse me of trying to make the data look better than they are. Some even imply that I am guilty of deception. Ah, well.) It is important to indicate in the figure/table legend, as well as in the methods, whether you are using standard deviation or standard error. Once you do choose, stick with your decision—do not alternate between standard deviations and standard errors. Whichever you decide, you must indicate the number of observations for each measurement so that the reader may convert from standard error to standard deviation (or vice versa).

Two final recommendations may be of use. First, after preparing a figure or table, find a member of your department who has a general understanding of the issues you hope to address but does not know the specifics of the study. Have the member explain to you what the material means. Further editing is required if there is ambiguity or misunderstanding. Second, follow the *Guide to Authors* for the journal to which you are submitting your work. Reviewers find it easier to comment on an article if it is formatted correctly, and often become grouchy if it is not. If you don't follow the formatting prescribed by the journal, changes may be made by a lay editor of the journal. If this person does not understand your work, its meaning may be altered.

References

References must accurately reflect what they are intended to represent. First, the reference should be appropriate to its purpose. "We confirm that isoflurane administration increases pituitary secretion (25)" may mislead if, in fact, reference 25 investigated the effect of enflurane on pancreatic secretion. A subtle variant of this problem is the quotation out of context and at variance with the intent of the previous investigator. Second, the obvious: The citation must be accurate. Of modest importance is the spelling of a name or title. Misspelling may lead to embarrassment and, occasionally, a strained relationship, but no great harm. However, an incorrectly stated journal, volume, or page can frustrate those trying to educate themselves. The reference usually can be found, but, sometimes, not without considerable effort. Such errors in reference also can have a life of their own! A second investigator (or the original investigator) may quote them without confirming their accuracy. Finally citation formats vary from journal to journal. The copy editor will bless you if you follow the format specific to the journal to which you submit your work.

Assumptions, Jargon, Abbreviations, and Acronyms

The reader is rarely as familiar with the topic of the paper as the author. Make as few assumptions as possible about the reader's background. The limitation on assumptions usually competes with the need for conciseness. Avoid the use of jargon, abbreviations, or acronyms in figures and tables, as well as in the text. Jargon should be avoided because it often is ambiguous and may not be understood (4). Abbreviations and acronyms, unless commonly accepted (e.g., EEG, ECG), distract the reader by requiring the remembrance of a nonsense word. Distraction increases exponentially with the number of acronyms or abbreviations. Also, the figures may circulate around the scientific community for many years (assuming your study to be of value). An abbreviation or acronym in vogue now may be out of style in 5 yr. If you *must* use an abbreviation or acronym, be consistent. (I have seen halothane abbreviated as "H" and "halo" in the same table. Pity the poor reader.)

Slides

Although a discussion of "slides" may not seem appropriate in a template describing the design of a paper, it is added because many slides are taken without alteration from the figures and tables prepared for a paper. In this era of easy graphics, much energy is devoted to making pretty slides with figurines, gorgeous colors, and diverse typesize and font. However, art for art's sake in a scientific paper is inappropriate. Pretty pictures may distract from the message you wish to communicate. Good data and clear presentations—not fancy graphics—win the hearts and minds of the viewers.

Keep the format consistent from slide to slide. The symbol for halothane in the first slide should also be the symbol for halothane in the second slide. This injunction also applies to figures for publication. It makes it easier for the viewer to follow your presentation. Also, choose one color format and stick to it. Don't shift from black on white to white on black to white on blue, etc. Black on white is the cheapest format, and slides using this format usually are more quickly made than colored formats.

Epilogue

The suggestions I've presented are just that, suggestions. Many papers follow a different pattern from the one I have outlined. However, investigators beginning their writing careers would be well advised to learn one approach and make it their own before passing on to different, and sometimes more elegant, approaches.

The following people shared their wisdom in the construction of this document: Dr. M. K. Cahalan, Dr. B. A. Cason, Dr. D. M. Fisher, Dr. G. A. Gregory, Dr. D. D. Koblin, Dr. N. A. Nussmeier, Dr. J. W. Severinghaus, Dr. R. B. Weiskopf, M. Zeiger, and W. von Ehrenburg.

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Clinical Reports

Continuous Spinal Anesthesia with a Microcatheter Technique: Preliminary Experience

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Key Words: ANESTHETIC TECHNIQUES, SPINAL.

Continuous spinal anesthesia has a long and interesting history. Dean (1) described the method at the 75th annual meeting of the British Medical Society in 1907 and discussed the relative merits of it and of inhalation general anesthesia. Currently, continuous spinal anesthesia is often reserved for use only in elderly patients and for lengthy operations because of the high incidence of postdural puncture headache (PDPH) when the currently available (large diameter) catheters are used in young patients (2). We have employed a 32-gauge polyimide microcatheter that threads through a 26-gauge spinal needle. It is therefore possible to provide continuous spinal anesthesia without increasing the incidence of PDPH. This report describes the evolution of the microcatheter, the problems encountered during its initial utilization, the intricacies involved with insertion and removal, and our results with 58 patients.

Materials and Methods

Fifty-eight adult patients scheduled for elective surgery were studied. Participation was voluntary and selection criteria excluded only patients with contraindications to spinal anesthesia. The protocol was approved by the Committee for the Protection of Human Subjects from Research Risks at the Brigham and Women's Hospital and written informed consent was obtained.

Materials

A 32-gauge, 36-in. (91 cm) polyimide catheter (Microspinal, TFX Medical, Duluth, Ga.) was tested and found to be nontoxic in laboratory animals. The inside diameter of the catheter was 0.2 mm (0.0079 in.) with a wall thickness of 0.0919 mm (0.00075 in.). A 35-in. (88-cm) stainless steel stylet 0.076 mm (0.003 in.) in diameter was employed to stiffen the catheter.

Procedure

The lumbar puncture site was prepared in an aseptic fashion. A 26-, 25-, or 22-gauge spinal needle was introduced into the subarachnoid space at the L2-3, L3-4, or L4-5 interspace. The 22-gauge needles, which are easier to manipulate, were used in elderly patients who were at lower risk for PDPH. After free flow of cerebrospinal fluid was obtained, the 32-gauge catheter with stylet was inserted 2–4 cm beyond the tip of the needle and the needle withdrawn.

Development of the microcatheter method went through three phases. In phase 1, the stylet was removed and a Tuohy–Borst adapter was attached to the free end of the catheter. In phases 2 and 3, the stylet was left in place to radiopacify and stiffen the catheter. In phase 3, a 20-gauge Teflon intravenous catheter (hereafter referred to as IV tubing to distinguish it from the microcatheter) 20 mm long was used as a threading aid (Figure 1).

Once inserted, the catheter was secured with a sterile transparent dressing and taped along the patient's back, and local anesthetic was injected. The subarachnoid location of the microcatheter was indicated by the rapid development of anesthesia. At the termination of the operation, the catheter was withdrawn. If resistance to removal was encountered, the patient was moved to the lateral, fully flexed position

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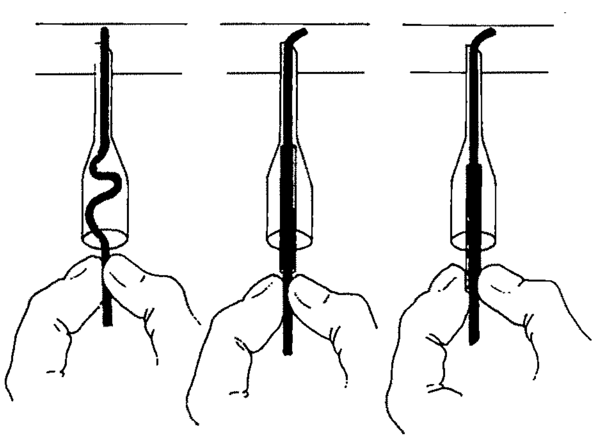

Figure 1. Because of the small diameter, the microcatheter may not be stiff enough to advance easily into the subarachnoid space (*left*). A 20 mm length of 20-gauge IV tubing passed over the microcatheter and into the needle hub provides lateral support to the microcatheter and enables advancement past minor obstructions (*center*). An alternative method (*right*) consists of "pinching" the IV tubing and microcatheter between the thumb and index finger before advancing the microcatheter.

to ease pressure on the microcatheter and to facilitate removal.

Results

The results of our experience with the microcatheter are presented according to the three developmental phases.

Phase 1

Twenty-four patients had the microcatheter inserted and the stylet withdrawn. The results in these 24 patients are shown in Table 1. A frequent problem was catheter kinking either below the skin surface or in skin folds under the tape. In addition, the stylet was often difficult to withdraw. One PDPH occurred in a 65-yr-old woman after diagnostic differential spinal block using a 26-gauge needle. This resolved without treatment. One catheter broke during removal in a 100-kg patient, leaving 5–6 cm of catheter in the patient. This patient had not been flexed as described in Methods when resistance to withdrawal was encountered. To date, there has been no morbidity associated with this occurrence.

Phase 2

The technique was modified by keeping the stylet in place, thus giving the catheter increased stiffness and radiopacity (Table 2). As the 0.076-mm stylet occupies approximately one-sixth the cross-sectional area of the lumen, it is possible to leave the stylet in place and inject around it. This modification produced increased stiffness, eliminating the problem of kinking seen in phase 1. During phase 2, 21 patients had continuous spinal anesthesia with the catheter stylet left in place. Postdural puncture headache did not occur in any of these patients.

Phase 3

In phases 1 and 2, it was often difficult to advance the catheter/stylet past the tip of the spinal needle into the subarachnoid space. Therefore, in phase 3, a 20-mm section of 20-gauge Teflon IV tubing was threaded over the spinal catheter to provide lateral support to the microcatheter in the needle hub during advancement (Figure 1). There were no failures in threading the catheter in 13 patients when the Teflon threading aid was employed (Table 3). One PDPH occurred in phase 3 in a 25-yr-old patient having a cesarean section. She required two 26-gauge dural punctures because of the accidental withdrawal of the microcatheter on the first attempt.

There were two cases of inadequate spinal anesthesia in phase 3. One occurred during repair of a large recurrent inguinal hernia. The operation was performed using local anesthetic infiltration. The second case involved a patient in whom bilateral vein ligation and stripping were performed. For reasons that are not clear, the patient had excellent anesthesia in all dermatomes with the exception of the left S1 nerve root. In an effort to improve the quality of anesthesia in both patients, more intrathecal local anesthetic was injected than would have been administered with a single-injection technique. Nevertheless, both patients had considerable motor power in the lower extremities at the conclusion of the operation, which indicates that distribution of the local anesthetic may have been restricted.

A second broken catheter occurred during phase 3 in a 72-yr-old man undergoing bilateral total knee replacements. The catheter had been inserted in an induction area. The catheter was secured with multiple pieces of tape running across (perpendicular to) the long axis of the body. No local anesthetic was injected as we were confident that the catheter was in the subarachnoid space. The tape and catheter were torn when they became stuck to the bed linens as the patient moved himself down the bed—leaving an unknown length of catheter fragment in the lumbar region. A second catheter was placed at the next

Table 1. Phase 1: 32-Gauge Microcatheter with Wire Stylet Removed

Patient's age (yr)	Patient's gender	Procedure	Local anesthetic	Needle gauge	Comments
75	F	Lower limb vascular	Bupiv 0.5%	26	*a, g*
75	M	Total knee replacement	Bupiv 0.5%	26	*a, g*
19	M	Sacral ulcer skin graft	Bupiv 0.5%	26	*a, g*
60	M	Penile implant	—	26	*c*
70	F	Transurethral resection of bladder tumor	Lido 5%	26	*a*
33	M	Inguinal hernia repair	Lido 5%	26	*a, b*
66	M	Lower limb vascular	Bupiv 0.5%	26	*a*
17	M	Total knee replacement	Bupiv 0.5%/lido 5%	26	*a*
68	F	Diagnostic spinal	Proc	26	*a, b, f*
31	F	Cesarean section	—	26	*h*
30	F	Cesarean section	—	26	*h*
24	F	Cesarean section	Bupiv 0.75%	26	*a*
33	F	Cesarean section	Lido 5%	26	*a*
31	F	Cesarean section	Bupiv 0.5%	26	*a*
30	F	Cesarean section	Lido 5%	26	*a*
23	F	Cesarean section	Lido 5%	26	*a*
40	F	Cesarean section	Lido 5%	26	*a*
27	F	Cesarean section	Lido 5%	26	*a*
35	F	Cesarean section	Bupiv 0.75%	26	*e*
27	F	Cesarean section	Lido 0.5%/fentanyl	26	*a, d*
36	F	Vaginal hysterectomy	—	26	*c*
65	M	Lower limb vascular	—	26	*c*
53	F	Lower limb orthopedic	Bupiv 0.75%	26	*a, g*
27	F	Lower limb orthopedic	Lido 5%	26	*a*

Proc = procaine, bupiv = bupivacaine, lido = lidocaine.

[a] Successful spinal anesthetic.

[b] Difficulty with threading but accomplished.

[c] Unable to thread catheter at all.

[d] Broken catheter.

[e] Catheter dislodged, not replaced.

[f] Postdural puncture headache.

[g] Unable to inject second dose because of kinking.

[h] Unable to withdraw stylet.

Totals: number = 24, successful = 18, difficulty threading = 2, unable to thread = 3, broken catheter = 1.

higher interspace and the 6-h operation was completed without further incident. This patient has had no morbidity from this occurrence.

Discussion

Advantages of continuous spinal anesthesia over single-dose spinal and continuous epidural anesthesia include the following. (a) Prior placement of the catheter in the induction area facilitates the surgical schedule. (b) Once the catheter has been inserted, spinal anesthesia may be induced after the patient has been positioned for surgery, thereby lessening the potential for hypotension associated with positioning the patient after induction of spinal anesthesia. (c) The low doses of local anesthetic intermittently injected virtually eliminate the possibility of systemic toxic reactions. (d) Repeated injection of small doses of local anesthetic solution increases the likelihood of obtaining exactly the right level of anesthesia and decreases the likelihood of cardiovascular instability during induction. (e) Employing a short-acting local anesthetic (lidocaine) shortens the recovery period. (f) The duration of anesthesia can be prolonged indefinitely, thus increasing anesthetic flexibility when the duration of surgery is uncertain. (g) A definite end point (aspiration of cerebrospinal fluid) assures that the catheter is in the right place and so enhances the likelihood of successful anesthesia. (h) Subarachnoid narcotics may be administered during a surgical procedure or continued into the recovery period to provide long-lasting postoperative analgesia.

The disadvantages of continuous spinal anesthesia are as follows. (a) Additional time is required to place the catheter in the right place, which may occasionally prove difficult. (b) Spinal headache is possible. (c) There is a potential for catheter breakage. (d) There is a potential for infection, nerve trauma, and hemorrhage (these potential complications have, however, rarely been documented in current clinical

Table 2. Phase 2: 32-Gauge Microcatheter with Wire Stylet in Place

Patient's age (yr)	Patient's gender	Procedure	Local anesthetic	Needle gauge	Comments
70	M	Lower limb vascular	Bupiv 0.5%	26	*a*
88	M	Sigmoid colostomy	Proc 5%	26	*a*
79	F	Lower limb vascular	Bupiv 0.5%/lido 2%	26	*a*
65	F	Closure leg amputation	Lido 5%/lido 2%	25, 26	*a*
87	F	Total hip replacement	Bupiv 0.375%	26	*a, b*
31	F	Cesarean section	Lido 5%	26	*a*
61	M	Lower limb vascular	Lido 5%	26	*a*
62	F	Total knee replacement	Bupiv 0.5%	26	*a*
76	F	Inguinal hernia repair	Lido 5%	26	*a*
36	F	Cesarean section	Lido 5%	26	*a*
77	M	Total hip replacement	Bupiv 0.375%	22	*a*
35	F	Bone marrow harvest	Lido 5%/lido 2%	26	*a, b*
25	F	Cesarean section	Lido 5%	26	*a, b*
59	M	Inguinal hernia repair	Bupiv 0.75%	22	*a*
18	M	Lower limb orthopedic	Bupiv 0.75%	25	*a*
31	F	Cesarean section	—	26	*c*
76	M	Inguinal hernia repair	Lido 5%	22	*a*
55	M	Lower limb vascular	Lido 5%	26	*a*
68	M	Ventral hernia repair	—	22, 26	*c*
26	F	Cesarean section	—	26	*c*
58	M	Lower limb vascular	Lido 5%	26	*a*

Proc = procaine, bupiv = bupivacaine, lido = lidocaine.
[a] Successful spinal anesthetic.
[b] Difficulty with threading but accomplished.
[c] Unable to thread catheter at all.
Totals: number = 21, successful = 18, difficulty threading = 3, unable to thread = 3.

Table 3. Phase 3: 32-Gauge Microcatheter with Wire Stylet in Place plus 20-Gauge Threading Aid

Patient's age (yr)	Patient's gender	Procedure	Local anesthetic	Needle gauge	Comments
62	F	Skin graft lower limb	Lido 5%/MS	25	*a*
60	M	Vein stripping	Lido 5%	25	*a*
36	F	Cesarean section	Lido 5%/fentanyl	26	*a*
25	F	Cesarean section	Bupiv 0.75%/MS	26	*a, b*
44	M	Anal sphincterotomy	Lido 1%/lido 2%	26	*a*
55	F	Total knee replacement	Lido 5%	25	*a*
55	M	Lower limb vascular	Lido 5%/lido 2%	25	*a*
40	F	Vaginal hysterectomy	Lido 5%/lido 2%	26	*a*
46	F	Vein ligation	Lido 5%/lido 2%	22	*a, c*
70	M	Inguinal hernia repair	Lido 5%/lido 2%	26	*a, c*
61	M	Lower limb vascular	Bupiv 0.5%/lido 5%/MS	25	*a*
68	M	Lower limb vascular	Lido 5%/lido 2%/MS	26	*a*
72	M	Bilateral total knee replacement	Lido 5%/lido 2%	25	*a, d*

Bupiv = bupivacaine, lido = lidocaine, MS = morphine.
[a] Successful spinal anesthetic.
[b] Catheter placed twice because of accidental removal on first attempt—patient had postdural puncture headache requiring epidural blood patch.
[c] Inadequate anesthesia.
[d] Broken catheter.
Totals: number = 13, successful = 13, difficulty threading = 0, inadequate anesthesia = 2, broken catheter = 1.

practice using catheters larger than the 32-gauge microcatheter).

The primary factor that has limited use of continuous spinal anesthesia is the belief that the large size of available spinal catheters requiring insertion through large spinal needles will result in an incidence of PDPH in young patients that is unacceptable (2). However, this contention is controversial. Denny et al. (3) recently reported the incidence of PDPH to be <1% (1 of 117 patients). The mean age of patients in this study having continuous spinal anesthesia in which an 18-gauge Hustead needle and a 20-gauge nylon epidural catheter were used was 63 yr. The authors postulated that an inflammatory reaction develops in the dura mater surrounding the puncture site, and that when the catheter is removed, edema or fibrinous exudate resulting from the inflammatory reaction seals the hole in the dura mater, thus preventing leakage of cerebrospinal fluid into the epidural space postoperatively. On the other hand, Bizzarri et al. (2) in 1964 employed a 20–21-gauge thin-walled spinal needle and a soft radiopaque catheter with a fine stylet. At the time, this was the smallest catheter used for continuous spinal anesthesia. It was constructed of polyethylene and had an outside diameter of 0.56 mm and an internal diameter of 0.25 mm. Later, Giuffrida et al. (4) employed this catheter in 74 patients having cesarean sections. The PDPH rate in these patients was 13%. More recently, Bizzarri (personal communication) found that with use of the 20–21-gauge needles and the fine-bore catheter, the PDPH rate in 535 patients was 9.35% overall, 13.2% in cesarean operations and only 0.77% (2 of 113) in patients having peripheral vascular surgery. The low incidence of PDPH in the vascular surgical patients is the same as that reported by Denny et al. (3). The mean age of Bizzarri's vascular surgical patients is not known, but we assume from the nature of their operations that they were in an age group similar to Denny's patients. Although our study population is small, the incidence of PDPH was approximately 4% (2 of 58). For comparison, the PDPH rate at the Brigham and Women's Hospital in obstetric patients who received single-injection spinal anesthesia using 26-gauge spinal needles was 6.5% (139 of 2132 patients). These data were obtained during the same time period that this microcatheter study was underway. Thus, the incidence of PDPH in our study and in that of Giuffrida et al. (4) was four to 13 times higher than reported by Denny. This is likely due to the fact that the mean age of patients in our report (50; range, 17–88 yr) and in Giuffrida's study (30; range, 17–45 yr) was less than that in Denny's study (63; range, 23–96 yr). Before we can accept the concept put forth by Denny et al. (3) that continuous spinal anesthesia with 17–18-gauge needles and epidural catheters results in a low incidence of PDPH in *all* patients, it must be demonstrated that this is in fact true in patients at highest risk, i.e., young patients and patients undergoing cesarean operation. Until this issue is resolved, we believe that PDPH is directly related to the size of the needle used for dural puncture, particularly in young patients. The use of 26-gauge needles and the 32-gauge microcatheter should, therefore, make continuous spinal anesthesia possible in young patients without increasing the incidence of PDPH over that seen with 26-gauge single-shot spinal anesthesia.

In addition to the two cases of PDPH, the microcatheter broke on two occasions. After neurosurgical consultation, it was decided not to retrieve the catheters (5). The patients were informed of the complication and, to date, neither has suffered any untoward effects. We believe that the microcatheter may become "trapped" in the ligamentum flavum. When resistance to removal of the catheter is encountered, flexion of the spine reduces the pressure on the catheter and facilitates withdrawal. By flexing the spine we have had no difficulty removing catheters. These 32-gauge microcatheters (tensile strength = 0.54 kg with stylet, 0.27 kg alone) employed in phases 1–3 were considerably weaker than 19-gauge Teflon epidural catheters (tensile strength = 1.58 kg). A new phase 4 microcatheter with a tensile strength of 1.18 kg is currently undergoing clinical trials. Careful attention to catheter protection—i.e., taping along the long axis of the body, minimizing patient movement, and careful positioning for the operation and during removal of the catheter—should minimize the potential for breakage.

Another concern was the two cases of inadequate anesthesia. This was most likely due to nonuniform distribution of the local anesthetic owing to the high resistance to injection that is associated with the microcatheter producing slow rates of flow as the local anesthetic exits the catheter tip. When nonuniform distribution occurs, use of solutions of differing density and altering the patient's position to "direct" the local anesthetic to the poorly blocked nerves may help. For example, if anesthesia is less profound on one side, injecting a hyperbaric solution and tilting the table toward that side will direct the local anesthetic to the poorly blocked nerves.

The overall complication rate during phases 1–3 was 20%; it included failure to thread the catheter, inability to inject local anesthetic, inability to withdraw stylet, inadequate anesthesia, PDPH, and two broken catheters. However, it must be appreciated that these complications occurred during the *development* of the microcatheter method. The problems of threading and the inability to inject or withdraw the stylet have been resolved with the threading aid and by integrating the catheter and stylet. Inadequate anesthesia and PDPH are expected occurrences during spinal anesthesia, per se, and appear to be neither more nor less common with the microcatheter technique than with single-injection spinal anesthesia. This leaves the complication of broken catheters. The increased tensile strength of the phase 4 catheter is expected to virtually eliminate this particular complication.

In summary, we have described the evolution of a

Comparison of a Transesophageal and Precordial Ultrasonic Doppler Sensor in the Detection of Venous Air Embolism

Donald A. Muzzi, MD, Thomas J. Losasso, MD, Susan Black, MD, and Rick Nishimura, MD

Key Words: MEASUREMENT TECHNIQUES, DOPPLER—transesophageal. EMBOLISM, AIR—detection.

Early detection and prompt treatment are important factors that limit morbidity and mortality secondary to venous air embolism (VAE) (1). The precordial Doppler ultrasonic sensor and transesophageal echocardiograph are the two most sensitive monitors currently available to detect VAE (2,3). The Aloka SSD-870 transesophageal echocardiograph is equipped with a Doppler sensor at the distal end of the probe, thereby providing Doppler ultrasound monitoring for VAE in addition to visual monitoring for VAE with echocardiography. Potential advantages in the use of the transesophageal sensor as opposed to a precordial Doppler sensor for monitoring of VAE are the following: (a) one is able to confirm the area within the heart that is being monitored by Doppler ultrasound; and (b) the quality of the Doppler signal is independent of external body habitus with the transesophageal Doppler sensor, in contrast to the precordial Doppler with which signal quality is very dependent on external body habitus (4). The purpose of our study was to compare the sensitivity of the precordial Doppler with the transesophageal Doppler sensor in detection of VAE.

Methods

With institutional review board approval ten patients who were undergoing neurosurgical procedures in the sitting position in which a transesophageal echocardiographic (TEE) probe was to be used were enrolled in the study. All patients had general anesthesia induced with thiopental and fentanyl. Muscle relaxation was achieved and maintained with vecuronium. All patients had their tracheas intubated and were placed on mechanical ventilation. Anesthesia was maintained with isoflurane and nitrous oxide/oxygen in a 1:1 mixture. Clinical monitoring included electrocardiogram, pulse oximeter, mass spectrometer, and indwelling arterial catheter. After induction of general anesthesia, all patients had a right atrial catheter inserted via the right or left basilic vein and localized at the junction of the right atrium and superior vena cava utilizing an electrocardiographic guided technique (5). A precordial Doppler stethoscope was placed over the right atrium. The position of the precordial Doppler was verified by injecting 5 mL of agitated saline through the right atrial catheter (6). A staff neuroanesthesiologist was responsible for verifying that the injection test was positive and that the precordial Doppler position was optimal. An Aloka SSD-870 TEE probe with a Doppler ultrasonic sensor at the tip was positioned to obtain a view of the right atrium and interatrial septum. The cursor on the screen that indicates the area being monitored by the TEE Doppler sensor was placed at the high right atrium or junction of the right atrium and superior vena cava. A controlled injection test utilizing 40 mL of agitated saline at a rate of 40 mL/min was performed three times on each patient. A staff neuroanesthesiologist noted when the injection test became positive on the TEE Doppler and on the precordial Doppler. An audible signal on any of the three injection tests in each individual patient was considered a positive test in each respective monitor. Visualization of micro air bubbles on the transesophageal echo was also noted (Table 1). Data were analyzed with a two-tailed Fisher exact test. Results were considered statistically significant if $P < 0.05$.

Results

The TEE Doppler sensor on the Aloka SSD-870 was more sensitive in detecting micro air bubbles elicited

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Table 1. Number of Injection Tests in Which Micro Air Bubbles Were Detected

Patient	TE Doppler	PC Doppler	TEE
1	3	0	3
2	3	0	3
3	3	0	3
4	3	0	3
5	3	0	3
6	3	2	3
7	3	0	3
8	3	0	3
9	3	0	3
10	3	0	3

TE, transesophageal; PC, precordial; and TEE, transesophageal echo.

by the controlled injection test than the precordial Doppler sensor ($P < 0.005$). The Doppler on the Aloka SSD-870 TEE probe detected a positive injection test in ten of ten patients (100%). The precordial Doppler detected a positive injection test in only one of ten patients (10%). In all ten patients we were able to visualize micro air bubbles secondary to the injection test with the Aloka SSD-870 TEE probe (see Table 1). No patient suffered any hemodynamic or neurologic consequences as a result of the injection test.

Discussion

It has been well established that early detection of VAE is enhanced with a precordial Doppler ultrasonic sensor (1). Although a precordial Doppler may be adequate in some patients, because of chest wall configuration, lung volume, or other unknown factors, the quality of Doppler sounds may be less than optimal (3,4).

Several clinical reports have demonstrated failure of a precordial Doppler to detect VAE that had been confirmed by other monitoring methods (3,7). Edmonds-Seal and Maroon (1), in a description of the precordial Doppler sensor, suggested that the esophagus might serve as an alternative site for Doppler sensor placement. In a study of dogs, the sensitivity of a TEE Doppler sensor has been shown to be equal to or greater than that reported for the precordial Doppler (8).

Our data indicate that the Doppler sensor on the Aloka SSD-870 is more sensitive in detecting micro air bubbles in venous blood from an injection test than is the precordial Doppler ultrasonic sensor. We also found that the TEE Doppler was clinically as sensitive as esophageal echocardiography in detecting VAE elicited from an injection test. The increased sensitivity of the TEE Doppler was more than likely related to its ability to remove chest wall configuration and lung volumes as confounding factors in transmission of an ultrasonic signal. The ability to visually place the TEE Doppler sensor directly in the high right atrium rather than indirectly (as done with the precordial Doppler utilizing the injection test) may also have enhanced its sensitivity in detecting VAE. Below the level of the fifth thoracic vertebra, the trachea is divided, and therefore there is no air column between the esophagus and surrounding vascular structures. The superior vena cava and right pulmonary artery lie anterior to the esophagus at the T-5 level, the superior vena cava and left atrium lie anterior to the esophagus at T-6, and the right and left atrium lie anterior to the esophagus at T-8 (9). Therefore the esophagus would seem to be an ideal location for placement of an ultrasonic sensor to detect VAE whether air was located in the superior vena cava, right atrium, or pulmonary artery.

In summary, the transesophageal Doppler sensor on the Aloka SSD-870 transesophageal echocardiographic probe was more sensitive than a precordial Doppler sensor in detecting VAE elicited from an injection test and was equally as sensitive clinically as the transesophageal echocardiograph.

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The Bullard Laryngoscope

A New Indirect Oral Laryngoscope (Pediatric Version)

Lawrence M. Borland, MD and Margaretha Casselbrant, MD

Key Words: INTUBATION, TRACHEAL—Bullard laryngoscope. EQUIPMENT, LARYNGOSCOPES—Bullard. ANESTHESIA, PEDIATRIC—intubation.

The Bullard laryngoscope (CIRCON ACMI, Stamford, Conn.) is a new combination fiberoptic and mirror instrument designed by Dr. Roger Bullard (former Director of Obstetrical Anesthesia at the Medical College of Georgia in Augusta, Ga.) to facilitate oral laryngoscopy and tracheal intubation of the difficult airway. It is classified as an indirect instrument because unlike conventional, direct instruments it uses mirrors and fiberoptic material to "look around a corner" at the larynx, rather than providing a direct view of the larynx. The endoscopist need not align the oral, pharyngeal, and tracheal axes in order to visualize the larynx. Thus, visualization of the larynx of a patient with severe micrognathia, a fixed temporomandibular joint, or limited cervical spine mobility is almost as easy as visualization of the larynx of a patient with a normal airway. Adult and pediatric versions of this laryngoscope have been developed concurrently. This is the first description of the pediatric prototype. We report its characteristics, advantages, and disadvantages.

The Instrument

Description

The Bullard laryngoscope (Figure 1) uses flexible fiberoptic bundles for both illumination and operator viewing, providing a 55° ± 5° field at the viewing tip. It weighs 1.2 kg without the illumination source. The blade is 1.3 cm wide, 13.2 cm long, and 0.64 cm thick at the viewing tip. A connection for a standard laryngoscope battery handle is provided; an adaptor and handle for use with high-intensity light sources are optional. Two operating channels are provided. The first has a Luer-lock connection for either O_2 insufflation, local anesthetic administration, or suction. The second channel accepts the Bullard intubating mechanism.

The Bullard intubating mechanism is a thumb-lever activated forceps that allows the operator both to advance the intubating forceps (and attached endotracheal tube) into the larynx and to release the endotracheal tube when properly positioned.

Technique

The technique used to introduce the Bullard laryngoscope blade is quite similar to that used for routine direct laryngoscopy. The endoscopist is positioned at the head of the patient as for standard oral laryngoscopy. The laryngoscope may be used by either a right- or left-handed individual. The mouth is opened manually by depressing the mandible with the thumb while stabilizing the head by counterpressure on the maxillary teeth. An opening of at least 0.64 cm is needed. The laryngoscope handle is rotated from the horizontal to vertical position and the blade slides around the tongue (Figures 2A, 2B). Once the handle is fully vertical, final placement may be facilitated by allowing the blade to drop momentarily to the posterior pharynx. The blade is then elevated up against the tongue's dorsal surface (Figure 2C). Only minimal upward movement exerted along the axis of the laryngoscope handle is required. The tip of the laryngoscope blade can be used to lift the epiglottis, but excellent visualization of the larynx is usually possible without this maneuver. The blade may also be placed in the vallecula, as is done with a Macintosh-type blade, but this is rarely necessary. The radiograph in Figure 3 demonstrates the final position of the laryngoscope blade.

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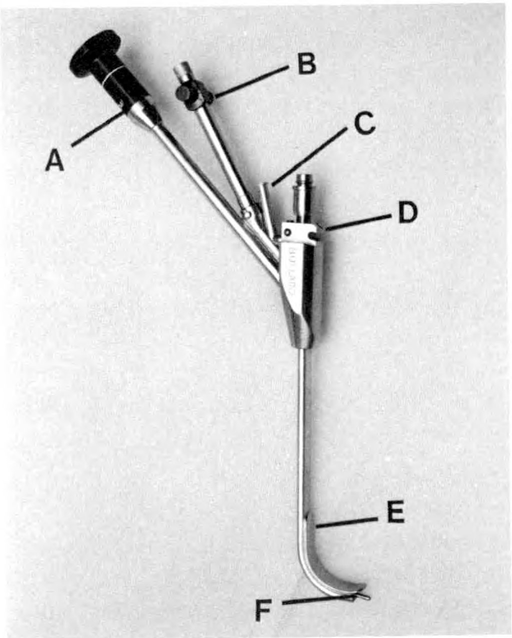

Figure 1. The Bullard laryngoscope. (A) Viewing eyepiece; (B) thumb-lever of intubating mechanism; (C) luer lock for suction, oxygen, or local anesthetics; (D) connection for standard laryngoscope battery handle; (E) anatomically shaped blade; and (F) viewing tip.

Intubation of the larynx is accomplished with either the Bullard laryngoscope's intubating forceps, a styletted endotracheal tube, or an endotracheal tube with a directional tip (e.g., Endotrol, Mallincrodt Critical Care, Glensfall, N.Y.). Before laryngoscopy the styletted endotracheal tube must be made to mimic the curve of the Bullard laryngoscope blade. After the larynx has been visualized, the tip of the endotracheal tube is introduced into the mouth next to the blade on either side and rotated into the mouth in a fashion similar to that for placement of the laryngoscope blade. Translaryngeal passage is guided and confirmed visually by the endoscopist. The stylet is then removed.

If the intubating forceps of the Bullard laryngoscope is used, an endotracheal tube with a "Murphy" eye is required. Before the laryngoscope is introduced into the patient's mouth, the endotracheal tube is loaded onto the laryngoscope (Figure 4), and the forceps withdrawn into the laryngoscope as far as possible. After the laryngoscope is introduced into the mouth and the larynx visualized, the thumb-lever is depressed, advancing both forceps and attached endotracheal tube. The endotracheal tube is then advanced between the vocal cords. The thumb-lever is depressed an additional 0.3 cm, and the jaws of the intubating forceps open to release the endotracheal tube, the tip of which is now subglottic. The endotracheal tube is advanced the appropriate intratracheal distance.

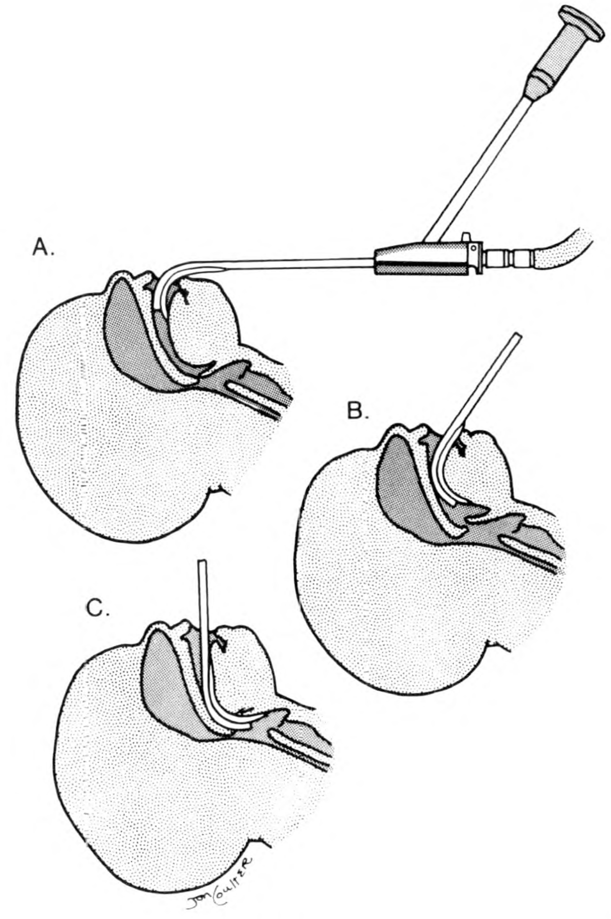

Figure 2. Introduction of the Bullard laryngoscope into mouth.

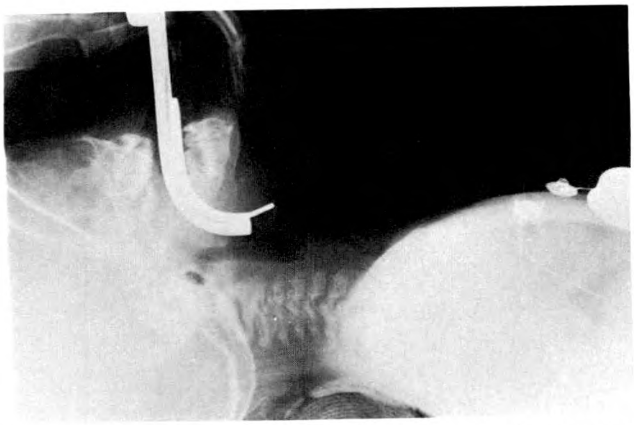

Figure 3. Radiograph of the Bullard laryngoscope in trial intraoral position.

Results

Using the Bullard laryngoscope, visualization of the larynx was attempted in 93 children (age, 2.1 ± 2.3 [SD] yr, range, 1 day to 10.7 yr; weight, 10.3 ± 6.0 kg, range, 1.2–29 kg). On the basis of history, physical

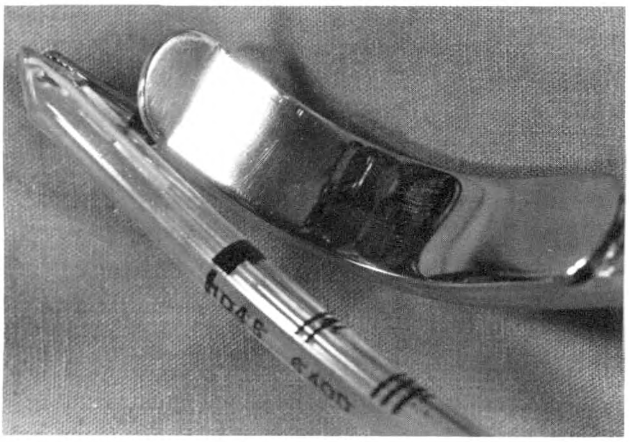

Figure 4. Endotracheal tube loaded onto Bullard laryngoscope intubating forceps.

Table 1. Patients with Abnormal Airways

Abnormality	Number
Pierre–Robin or Stickler's syndrome (micrognathia, glossoptosis, cleft palate)	10
Trisomy-21	2
Cornelia de Lange syndrome	2
Unstable cervical spine (including one patient with Pierre–Robin syndrome)	2
Isolated micrognathia	4
Craniofacial syndrome (undefined)	5
Macroglossia	1
Treacher–Collin's syndrome	1
Noonen's syndrome	1
Klippelfel–Weil syndrome	1
Alpert's syndrome	1

examination, and/or review of previous anesthetic records, 29 (31%) patients presented with potential or previous difficulty in achieving successful laryngoscopy (Table 1). Laryngoscopy was successful in 90 cases (97%). Two failures occurred as a result of excess secretions. The third failure is described below.

Proficiency in the use of this laryngoscope (i.e., full visualization of the larynx on the first laryngoscopy) was established by the third time it was used. Time to full visualization of the larynx in 50 anesthetized patients (by the primary author) was 12.6 ± 6.5 s; range, 6–45 s. The longest time needed for laryngoscopy occurred in an infant with a long, floppy epiglottis. Laryngoscopy in this infant was interrupted twice because of oxygen desaturation; therefore, laryngoscopy and intubation times were not included.

Tracheal intubation was attempted in 15 patients and successful in 14 (93%). Tracheal intubation in five (33%) within this group had previously been either very difficult or impossible. The one unsuccessful intubation with the Bullard laryngoscope occurred in a premature infant with severe micrognathia, glossoptosis, micro-os, and cleft palate. Although the larynx was immediately and easily visualized with the Bullard laryngoscope, the small size of the mouth did not allow adequate room to direct and place the endotracheal tube. Subsequent attempts with both a routine and an anterior commissure laryngoscope using a Storz–Hopkins zero-angle light rod also failed to visualize the larynx.

Awake laryngoscopy was performed in 17 infants of the patients in this series with excellent visualization and with no distortion of the epiglottis and larynx. The Bullard laryngoscope appears to cause less discomfort in the awake patient than routine direct laryngoscopy. The evaluation of the Bullard laryngoscope for diagnostic awake laryngoscopy is the subject of a separate report.

Discussion

Laryngoscopy and tracheal intubation in the newborn and older infant may be difficult because the tongue is large relative to the oral cavity, the epiglottis is U-shaped (in the youngest children), and the larynx is placed cephalad. Visualization of the larynx may be difficult or even impossible in cases of immobility or instability of the cervical spine, macroglossia, micro-os, certain craniofacial deformities, or temporal-mandibular abnormalities such as the Pierre–Robin syndrome.

The Bullard laryngoscope provides the clinician with an alternative to routine direct oral laryngoscopy because it does not require alignment of the oral, pharyngeal, and tracheal axes.

We evaluated this instrument in 64 infants and children with normal airway anatomy and in 29 with abnormal upper airway anatomy. In 90 patients the Bullard laryngoscope (pediatric prototype) made laryngoscopy quite easy and fast. As with any fiberoptic instrument, when excess secretions, blood, or vomitus is present in the oral cavity, visualization may be difficult. In two patients early in the series visualization was unsuccessful because of excess secretions. The appropriate use and timing of an antisialagogue and oral-nasal suctioning are important components of this technique. A third patient experienced oxygen desaturation during a difficult laryngoscopy because the earliest prototype laryngoscope did not have an oxygenation channel. This channel is now present in all production models.

Because this instrument requires a mouth opening of only 0.64 cm in the cephalad-caudal axis, it may be easily introduced without trauma in extremely small infants. We used it successfully in a premature infant weighing 1.2 kg. As it combines fiberoptic technology with oral laryngoscopy (unlike nonroutine techniques to manage the difficult airway), proficiency with the Bullard laryngoscope may be easily achieved by an individual skilled in routine direct laryngoscopy.

In summary, the unique features of the Bullard laryngoscope simplify management of the difficult pediatric airway while avoiding the steep learning curve required with flexible fiberoptic devices.

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Anesthetic Implications of Zenker's Diverticulum

Somasundaram Thiagarajah, MD, FFARCS, Erwin Lear, MD, and Margaret Keh, MD

Key Words: GASTROINTESTINAL TRACT, ESOPHAGUS—Zenker's diverticulum.

Zenker's diverticulum, seen in 1 of 800 upper gastrointestinal barium studies (1), consists of an outpouching of the pharyngeal mucosa through the posterior wall of hypopharynx and was first described by Zenker and Von Ziemssen in 1874 (2). The diverticulum tends to occur in elderly patients, the age at which coronary artery disease is common (3), and may often be associated with recurrent aspiration pneumonitis and malnutrition (4). The implications for the anesthesiologist and the potential for perioperative complications in patients presenting for surgical resection of their Zenker's diverticulum have not been reported previously. We report a case to underscore possible complications and the salient features of the disease based upon a review of the literature and the experience gained in the anesthetic care of 33 patients with Zenker's diverticulum (Table 1).

Case Report

A 74-yr-old man was scheduled for resection of a large Zenker's diverticulum that extended into the upper mediastinum. His symptoms included dysphagia, regurgitation of food, gurgling noise in the throat, and bouts of coughing on lying down.

On physical examination, he was 160 cm in height and weighed 47 kg. Blood pressure was 130/70 mm Hg with a heart rate of 78 beats/min. He was breathing 20 times per minute and his temperature was 36.5°C. Preoperative laboratory data and the electrocardiogram were reported as normal. Chest x-ray revealed a sizable diverticulum in the upper mediastinum.

The patient was premedicated with 25 mg IM hydroxazine 90 min before induction of anesthesia. On arrival in the operating room, the patient was encouraged to regurgitate the diverticular contents. On the operating table he was positioned with 10° head up and oxygen was administered via a face mask. Anesthesia was induced with 100 μg IV fentanyl, 75 mg lidocaine, and 200 mg thiopental. The trachea was intubated with a 7.5-cm (internal diameter) Portex endotracheal tube after achieving relaxation with 80 mg of succinylcholine. The tracheal cuff was inflated to achieve an airtight seal. Pressure was applied to the cricoid cartilage during induction of anesthesia until the cuff of the endotracheal tube was inflated. There were no food particles or fluid in the oropharynx during intubation. The lungs were clear to auscultation immediately after intubation and throughout the operative course. Anesthesia was maintained with 50% nitrous oxide in oxygen and isoflurane. Intraoperatively, at the request of the surgeon, a 38 F bougie was placed in the esophagus to help in identification of the diverticulum. The resection was carried out through an incision in the neck. After excising the diverticular sac, the suture lines on the pharyngeal wall were tested for air leaks. The operation lasted ~70 min. At the end of surgery, with the patient awake and responsive, the trachea was extubated.

On admission to recovery room, the patient was tachypneic (breathing 26 times per minute) and restless. A chest x-ray revealed a right mid- and upper zonal density (Figure 1) and an arterial blood sample obtained while breathing 40% oxygen via face mask had a pH of 7.38, Pa_{O_2} of 67 torr, and Pa_{CO_2} of 42 torr. Blood pressure was 180/90 mm Hg and heart rate 72 beats/min. He was closely observed for signs of increasing respiratory distress and had frequent chest physiotherapy. The chest x-ray on the next day showed the density in the right upper and middle lobes to have decreased in size; arterial blood had a pH of 7.39, a Pa_{O_2} of 100 torr, and a Pa_{CO_2} of 40 torr while breathing 40% oxygen by face mask. The sub-

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Table 1. Zenker's Diverticulum Resection (1981–1988)

	Number of patients (n = 33)
Age group: 62–80 yr (70±2)	
Sex	
Female 30%	
Male 70%	
Associated medical diseases	
Coronary heart disease	7
Weight loss	3
Recurrent aspiration pneumonitis	3
Average size of diverticulum (cm)	
Length 2.8 ± 0.75	
Width 2.8 ± 0.5	
Anesthetic technique for intubation	
Awake intubation	6
General anesthesia	
With cricoid pressure	6
Without cricoid pressure (not documented)	21
Postoperative complication: respiratory distress due to spillage into lung lobes	1

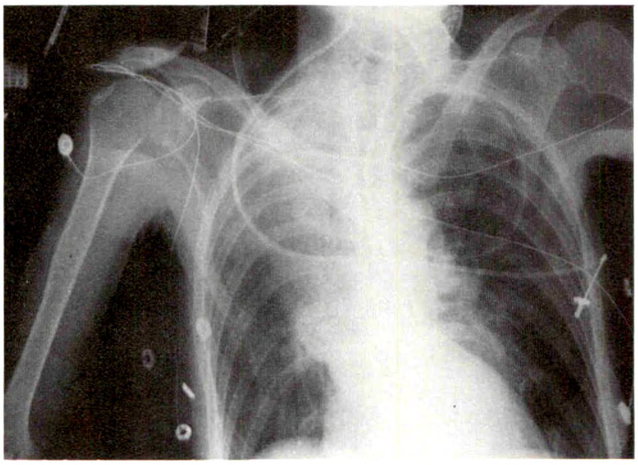

Figure 1. Chest x-ray showing right upper and mid-zonal opacities immediately after surgery in the recovery room.

sequent hospital course was uneventful and the patient was discharged on the fifth postoperative day.

Discussion

The pharynx, extending 12–14 cm from the base of the skull to the lower border of the cricoid cartilage (C-6), is composed of skeletal muscle forming superior, middle, and inferior constrictors. The inferior constrictor has two components, the thyropharyngeus and cricopharyngeus muscles. The cricopharyngeus has an oblique and horizontal component with an area of muscle weakness between these two groups of muscles (Killian's dehiscence). The Zenker's diverticulum is an outpouching of the mucosa that develops in this weak area. Early symptoms may be nonspecific with complaints of food sticking in the throat and increased swallowing time. The sac frequently enlarges with time and may be associated with noisy swallowing, regurgitation, and bouts of coughing when lying down. Compressible swelling may develop as the sac enlarges. Recurrent pneumonia and lung abscess may develop in later stages. X-rays of the neck may disclose a collection of air anterior to the fifth and sixth cervical vertebrae. A barium swallow examination is usually diagnostic. Treatment is surgical. The sac is identified by a lower collar skin incision and after retracting the sternocleidal muscle and the carotid contents the sac is identified, dissected from the esophagus, and resected.

Compromised cardiovascular, pulmonary, and nutritional states are problems often seen in patients with Zenker's diverticulum (4). Recurrent aspiration of food particles from this pouch into the pharynx may lead to pneumonitis or even lung abscess formation (4). Dysphagia frequently causes malnutrition with resultant hypoproteinemia and muscle wasting. In the preoperative preparation, nutritional and pulmonary status must be evaluated.

The presence of a diverticular pouch in the pharynx poses a number of problems for the anesthesiologist. Oral premedications are not suitable as the tablets may get lodged in the pouch and either be ineffective or be aspirated into the lungs (5).

Regurgitation of liquid or solid material from the pouch into the lungs during anesthetic induction is the major concern for the anesthesiologist. If the aspirate is solid, atelectasis with resultant hypoxemia and infection will ensue. If the aspirate is liquid, the infective material in aspirate may cause pneumonia.

The secretions in the pouch tend to be alkaline, similar to saliva, and therefore chemical pneumonitis is unlikely to develop; antacids are of no value. Regurgitation may also occur during induction of anesthesia, during intubation, or even after successful intubation due to seepage of fluid around the cuff of the endotracheal tube during surgical manipulation. In the above case, aspiration did not occur during induction or intubation but most likely occurred during surgical manipulation. Therefore, fasting before surgery is extremely important. Voluntary, self-induced regurgitation of food by the patient before induction should be encouraged; this may empty the pouch. Awake intubation has been advised (4). Cricoid pressure may or may not be effective depending on whether the body of the sac is at the level of cricoid cartilage (Figure 2). If the sac is

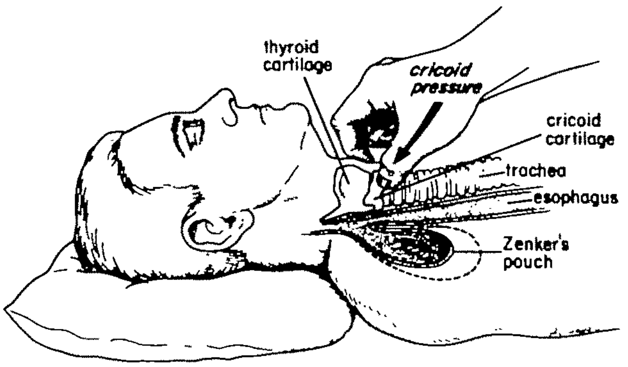

Figure 2. The Zenker's pouch in the hypopharynx, with the opening at the level of cricoid cartilage.

small, the body of the pouch will be at the level of the cricoid cartilage in which case cricoid pressure will compress the body of the pouch, spilling the contents into the pharynx. If the sac is large, the neck of the pouch will be under the cricoid cartilage and cricoid pressure will not empty the pouch. Once the endotracheal tube is in place, a moist gauze pack placed to surround the tube will prevent regurgitation during surgery.

Perforation of the diverticulum is another potential complication. If a nasogastric tube is inserted, caution and gentleness must be exercised; during a difficult intubation, blind attempts at intubation of the trachea may perforate the pouch resulting in mediastinitis.

As in any surgery of the neck, blood loss and air embolism may occur if major vessels are inadvertently severed and with retraction of the carotid sheath the baroreceptors may initiate tachyrhythmia or bradyarrhythmias.

During 1981–1988 in our institution 33 patients had surgical resection of Zecker's diverticulum under general anesthesia. Premedications were administered parenterally. Before induction of anesthesia, voluntary emptying of the diverticula was encouraged. The significant associated medical disorders are summarized in Table 1.

The anesthetic techniques for tracheal intubation varied depending on the size of the diverticulum. Patients with diverticula that extended into the mediastinum were either intubated awake or after intravenous induction with cricoid pressure. The patient presented in this case history had respiratory distress owing to the spilling of diverticular contents into the lungs most probably during surgical manipulation.

In summary, patients with Zenker's diverticulum may have cardiac and pulmonary complications and suffer from malnutrition. Review of the patient's barium swallow x-ray will indicate the size and the position of the pouch opening. Voluntary, self-induced emptying of the pouch before induction, gentleness during intubation, and packing around the endotracheal tube will minimize spillage of pouch contents into the pharynx and decrease the risk of aspiration.

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Prevertebral Hematoma Secondary to Whiplash Injury Necessitating Emergency Intubation

Lloyd Biby, MD and Albert H. Santora, MD

Key Words: INTUBATION, TRACHEAL—prevertebral hematoma. SURGERY, NEUROLOGIC—cervical spine trauma.

Whiplash is defined as an acute sprain or an acceleration extension injury of the cervical spine (1). Hyperextension and hyperflexion of the neck can cause various types of injury, some of which can be severe, ranging from cervical fractures to ligamentous disruption. Cervical hematoma is quite an unusual complication after whiplash injury. Cervical hematomas large enough to require emergency intubation are rare and to our knowledge have not been reported previously.

Case Report

A 27-yr-old woman was brought to the emergency clinic after a high-speed automobile collision. She had experienced loss of consciousness and had required a short period of ventilatory assistance by mask. Her cervical spine had been immobilized at the scene of the accident. During transit, she had remained hemodynamically stable.

On arrival in the emergency room her vital signs were stable with a respiratory rate of 24. Neurologic examination revealed an awake, alert, oriented patient who could move all extremities. All cranial nerves were intact except for a left sixth nerve palsy. The trachea was in the midline. The soft tissues of the neck were tender to palpation both anteriorly and posteriorly along the spinous processes. The chest was clear and the heart had a regular rate and rhythm. Abdominal examination was noncontributory. The neurosurgical assessment was as follows: (a) probable closed head injury; (b) new onset sixth cranial nerve palsy; and (c) questionable cervical spine fracture. The surgeon recommended continuation of strict cervical spine immobilization, head computed tomography (CT) scan, and cervical spine CT scan to evaluate the odontoid process. All laboratory values were within normal limits.

Computed tomography scan of the cervical spine in the emergency department revealed no bony abnormalities. However, severe prevertebral soft tissue swelling suggested a hematoma, a finding often associated with an odontoid fracture.

Immediately after completion of the CT scans, the patient began complaining of severe dysphagia and neck pain. Evaluation in the operating room revealed a thin, crying woman with an immobilized cervical spine. Temporomandibular joint motion was decreased to 1.5 cm secondary to trismus. Her uvula could not be visualized. Her nares were patent without signs of epistaxis or rhinorrhea. Breath sounds were equal bilaterally. After consultation with the radiologists and neurosurgeons, it was clear that an endotracheal tube should be inserted as soon as possible because of the risk of impending airway obstruction from the expanding cervical prevertebral hematoma. Surgeons from the Ear, Nose, and Throat Department were standing by ready to perform a tracheostomy if necessary. The nasal mucosa was vasoconstricted with phenylephrine spray and topically anesthetized with 10% lidocaine spray and lidocaine-soaked pledgets. Her tongue and pharynx were sprayed with 10% lidocaine. A fiberoptic bronchoscope was passed nasally. The upper airway anatomy was found to be distorted by a posterior soft tissue swelling that extended from oropharynx to the glottis. The glottic structures were normal. A 7.0-cm endotracheal tube was passed over the bronchoscope with no discomfort to the patient. After intubation, the patient remained alert, cooperative, and neurologically intact. The patient was admitted to the neurosurgical intensive care unit where she was observed for several days. A review of all x-rays and CT scans documented marked prevertebral he-

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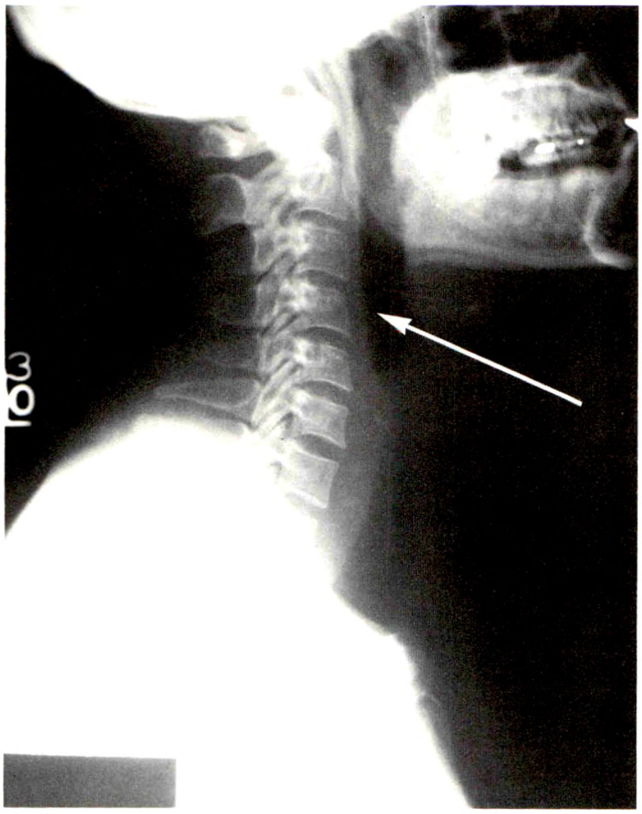

Figure 1. The *arrow* points to the prevertebral plane in a lateral radiograph of a normal patient. The width of this plane is normally 3.2 mm at C-2.

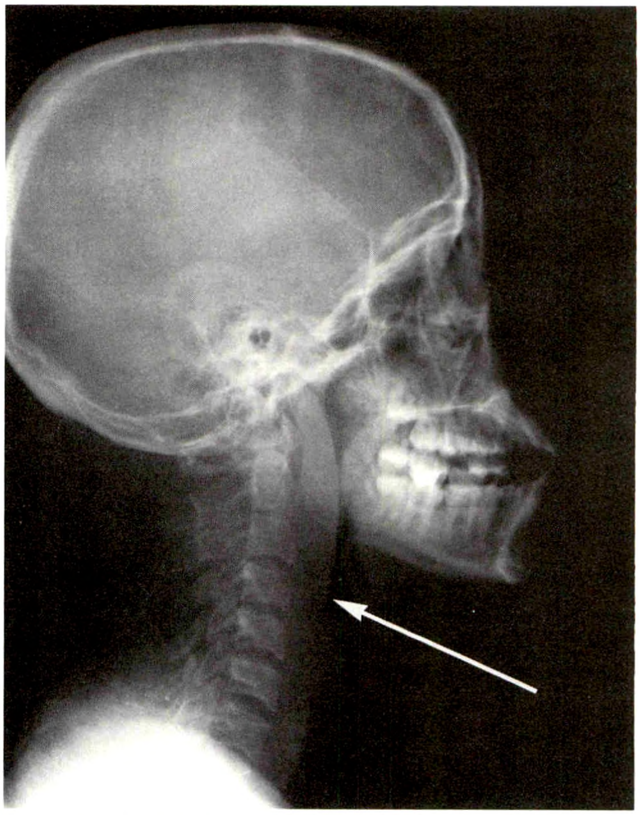

Figure 2. The *arrow* points to the prevertebral plane in a lateral radiograph of the patient presented in this report. The width of the plane measured 11 mm at C-2.

matoma formation and no fracture or ligamentous injury.

On subsequent days, no air leak was noted when the endotracheal tube's balloon was deflated, suggesting residual supraglottic swelling. Finally, on the 12th day after admission, with the patient under general anesthesia, the tracheal tube was removed after direct laryngoscopic examination of the airway revealed that the soft tissue swelling had resolved.

Discussion

Airway obstruction from prevertebral hematoma formation should be considered in patients presenting with whiplash or related neck injuries. Penning (2) reported that 18 of 30 patients hospitalized for cervical spine injuries had widening of the prevertebral soft tissue due to hematoma. Of these 30 patients, 10% had hyperextension sprain or whiplash as the mechanism of injury. The majority of the hematomas occurred at C1-4. The normal width of the prevertebral soft tissue is 3.2 mm measured at C-2. In our patient the width of prevertebral soft tissue at C-2 was 11 mm. Penning also reported that radiographic resolution of the prevertebral hematomas occurred within 14 days. Figures 1 and 3 show the normal prevertebral soft tissue on a lateral cervical spine x-ray and neck CT scan and Figures 2 and 4 as seen in our patient.

One previous report recognized that hematomas secondary to cervical vertebrae injuries could possibly lead to airway compromise but elaborated no further (3). Previous surgical case reports (4,5) described airway obstruction caused by hangman's fractures that were relieved by tracheostomy, but offered no explanation as to the etiology of the airway obstruction.

Management of patients with whiplash or other cervical injuries has focused on the importance of neck immobilization; however, recent literature (6) suggests that traditional mechanisms to stabilize the neck may in fact fail to do so. Therefore, it is important for the anesthesiologist to take precautions during intubation to protect the spinal cord. To this end, oral or nasal fiberoptic intubation has become a mainstay in the management of patients with cervical spine injuries. In the case reported, awake nasal fiberoptic intubation was utilized to establish and secure airway patency. An oral fiberoptic intubation

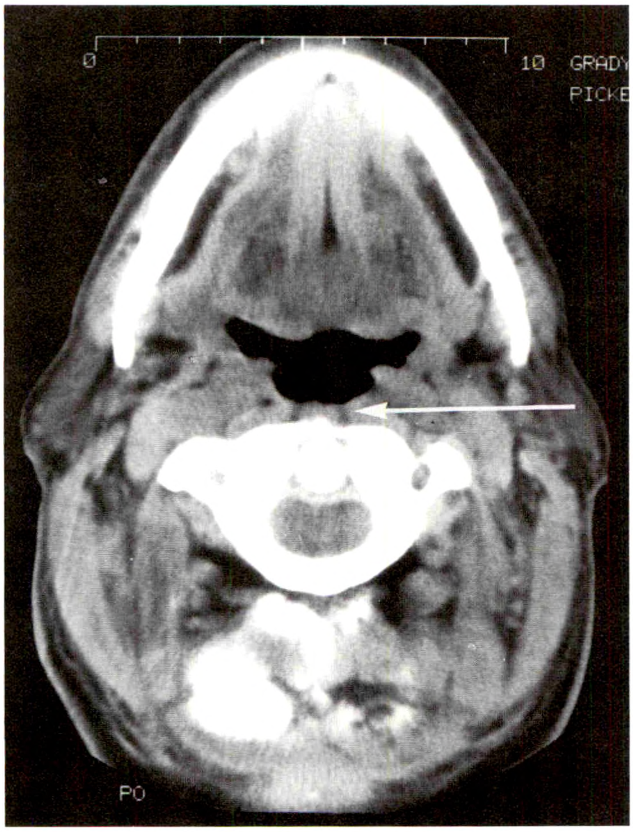

Figure 3. The *arrow* points to the prevertebral plane on a CT scan of a normal patient at the level of the odontoid.

would have been attempted if the patient had signs or documentation of nasal or basilar skull fractures, or if it was believed that a nasal approach might rupture the hematoma.

In conclusion, this case illustrates a potentially life-threatening airway emergency that resulted from a severe form of a common injury, whiplash. The possibility of airway obstruction from an expanding prevertebral hematoma must be considered in patients who have suffered hyperextension injuries to the cervical spine.

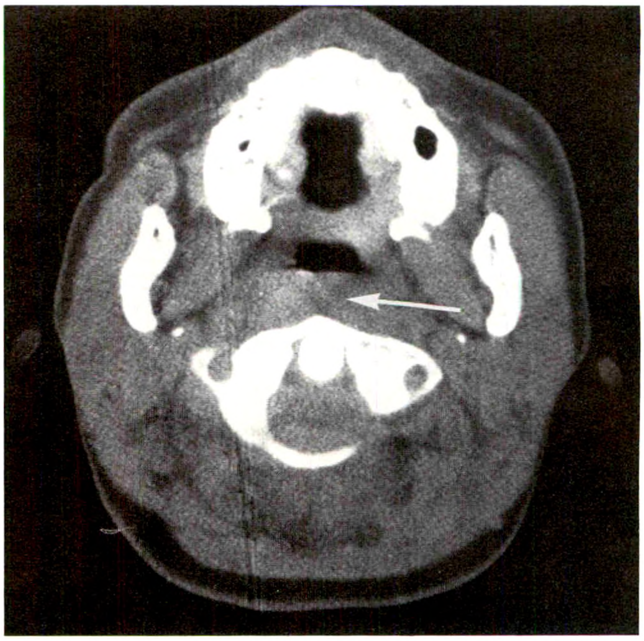

Figure 4. The *arrow* points to the prevertebral plane on a CT scan of the patient presented in this report.

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Letters to the Editor

Diagnosis of Malignant Hyperthermia in Infants

Key Words: HYPERTHERMIA, MALIGNANT.

To the Editor:

We read with interest the clinical report by Wilhoit et al. (1) describing a 7-wk-old male infant who developed acute rhabdomyolysis on exposure to halothane and succinylcholine. Subsequent muscle histopathology was consistent with Duchenne's muscular dystrophy (DMD). There are several points here that deserve comment.

First, based on the observed elevation of creatine kinase (CK)-MB isoenzymes in their patient, the authors discussed the possibility of myocardial damage secondary to DMD or malignant hyperthermia (MH). In fact, CK-MB elevation is commonly seen in DMD and can be traced to skeletal muscle in origin (2,3). This would help to explain why the infant had no cardiovascular instability and a normal echocardiogram.

The authors question the effect of the relatively large dose of succinylcholine in terms of muscle membrane depolarization triggering MH. A recent study by Iaizzo et al. (4) showed that halothane-induced contractures in MH-susceptible porcine muscle are not associated with membrane depolarization. This suggests that membrane depolarization is not necessary for MH triggering.

In vitro contracture testing would not be indicated in this child for two reasons. First, the amount of muscle required would leave a visible defect in the muscle belly. Second, control data from infants are lacking for comparison (5), making it difficult to interpret the results of the test. Generally, children under 4 yr of age or 20 kg body weight are not considered eligible for MH muscle biopsy.

The relationship between the genetic inheritance of MH and DMD is not well understood (6). Whereas DMD is an X-linked disorder (3), MH usually follows an autosomal dominant pattern (7). Although DMD patients may develop anesthetic-induced rhabdomyolysis, this may not be true of their close relatives. For this reason we recommend that the parents of such DMD patients be tested for MH. It is possible that the parents and unaffected siblings of such DMD patients are not at increased risk for MH. Obviously, this would be of importance to such families.

Finally, in children who have had an adverse anesthetic reaction that may be due to a neuromuscular disease, the Muscular Dystrophy Association (MDA) may be able to provide financial assistance to some families. The MDA will cover MH testing in selected cases, provided that other tests, e.g., histopathology, are also performed. Several children with MH or other myopathies have been tested in our laboratory with the support of the MDA.

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In Response:

We thank Dr. Allen and Dr. Rosenberg for their response to our article (1).

We agree that patients with DMD often have elevated levels of CK with an abnormal level of the MB fraction. This CK elevation involving both MM and MB fractions appears to have its origin largely in the skeletal muscle (2). Mayhew et al. (3), however, found a 5.8% level of the MB isoenzymes of CK after an episode of MH in a 6-mo-old infant who did not have DMD. The origin of the MB fraction of CK in the infant reported by Mayhew et al. is unknown, but was probably either skeletal or cardiac muscle. Gronert et al. (4) observed that the heart undergoes major stresses during an episode of MH secondary to electrolyte and sympathetic nervous system stimuli. The 7-wk-old infant

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whose case we reported had evidence of some acute myocardial involvement evidenced by two brief episodes of ventricular tachycardia and several premature ventricular contractions (1). We agree that the elevation of the MB fraction of CK in the infant we cared for may well have been from skeletal muscle, but we cannot completely rule out some contribution from cardiac muscle.

Iaizzo et al. (5) have shown that halothane does not depolarize MH-susceptible muscle of swine. They did not, however, evaluate succinylcholine, which is well known for producing depolarization and triggering MH in swine skeletal muscle (4). As Gronert et al. (4) postulated in their recent review, calcium is released into the muscle cytoplasm by perhaps more than one mechanism, thus triggering MH. Under this assumption, both depolarization and halothane's mechanism of action could trigger MH episodes.

We fully agree that this child is too young to undergo in vitro contracture testing, and that in vitro MH susceptibility testing should be performed on the child's parents. We hope that financial assistance from an agency such as the MDA will provide the impetus needed for testing.

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Drug Infusions: Drips by Drops

Key Words: ANESTHETIC TECHNIQUES, INTRAVENOUS—infusions. PHARMACOKINETICS, INTRAVENOUS INFUSIONS.

To the Editor:

The infusion of drugs is commonplace in anesthesiology and critical care. Although guidelines for drug dilutions and dosage rates have been suggested (1), the sheer number of drugs available for continuous intravenous infusion makes specific drug dilutions and infusion protocols difficult to remember. Nonstandard dilutions (2), formulas (3), and nomograms (4,5), to say nothing of programmable

Table 1. Drug Dilutions, Infusion Rates, and Dosage Ranges

Drug	Supplied ampule (mg)	Diluted in 250 mL (μg/mL)	Infusion rate (μg/min)			Adult dose range ($\mu g \cdot kg^{-1} \cdot min^{-1}$); ($\mu g \cdot 70\ kg^{-1} \cdot min^{-1}$)
			Low (15 mL/h)	Medium (30 mL/h)	High (60 mL/h)	
Adrenergic						
Catecholamines						
Dopamine[a]	200	800	200	400	800	2.5–20; 175–1400
Dobutamine	250	1000	250	500	1000	2.5–10; 175–700
Isoproterenol[b]	1	4	1	2	4	Titrate to effect
Epinephrine[b]	1	4	1	2	4	Titrate to effect
Norepinephrine[b]	4	16	4	8	16	Titrate to effect
Noncatecholamines						
Phenylephrine	10	40	10	20	40	Titrate to effect
Nonadrenergic						
Theophylline[c]	250	1000	250	500	1000	3.5–16; 250–1000
Hypotensives						
Sodium-nitroprusside[d]	50	200	50	100	200	0.5–10; 35–700
Nitroglycerine	50	200	50	100	200	0.5–10; 35–700
Trimethaphan	500	2000 (2 mg/mL)	500	1000	2000	5–70; 350–5000
Antidysrhythmics[e]						
Lidocaine/procainamide/bretyllium	1000 (1 g)	4000 (4 mg/mL)	1 mg	2 mg	4 mg	1–4 mg/min

[a] Dopamine is commonly available in 400 mg/ampule; dilute in 500 mL.
[b] Low, medium, and high doses as recommended, but titration may necessitate different ranges.
[c] Requires loading dose. Infusion rate's range usually given in hours: 0.2–1 ($mg \cdot kg^{-1} \cdot h^{-1}$).
[c] Toxicity likely after 30 min in higher ranges.
[d] Lidocaine commonly available in 2-g ampule; dilute in 500 mL. All require loading dose.
[e] Bretyllium dose range is 1–2 mg/min.

calculators with data banks and dedicated infusion pumps, have been proposed to facilitate the preparation, administration, and dosage calculation of intravenous infusions.

Reliance on any of these methods presents several problems. Tables and "infusion calculators" are not always available for quick reference when needed. Also, these methods are so complex that one may neither memorize nor teach the tables and formulas to colleagues. Furthermore, the use of tables based on nonstandard dilutions results in great waste and has a large margin of error. Finally, expediency may preclude the deliberation and time necessary to consult dilution tables and set up infusion pumps.

A nearly ideal method of drug dilution and delivery would obviate reliance on memorization, tables, and calculators. It would require little experience to quickly prepare and administer "drips" accurately. Such a method simply involves diluting an ampule of drug in one 250-mL bag of crystalloid or fluid. Infusion rates of 60, 30, and 15 mL/h result in "standard" dosages for high, medium, and low ranges, respectively, for a 70-kg person. When an infusion pump is not available, a "microdrip" (commonly 60 drops = 1 mL) can be used and easily set manually at 1 drop/s (60 mL/h or 1 mL/min), 1 drop/2 s (30 mL/h), or 1 drop/4 s (15 mL/h), and the respective high, medium, and low dosage ranges are thus achieved with little effort. The dilute solutions used will result in easy titration without exaggerated effects.

For adults who do not weigh 70 kg, these numbers can be altered by appropriate percentages. However, these "low, medium, and high" dosages can be readily used to initiate most adults' infusions as finer dosage adjustment is based on titration to effect. The volumes utilized (up to 60 mL/h) make this dilution inappropriate in infants and neonates.

Calculating the dilutions and delivered dose is accomplished through the use of simple arithmetic. The milligrams of drug added to 250 mL multiplied by four equals the micrograms per milliliter ($4 \times [\text{mg}/250\ \text{mL}] = \text{mg}/1000\ \text{mL} = \mu\text{g/mL}$). The micrograms per milliliter also equals the micrograms per minute administered when the infusion rate is set at 60 mL/h (1 mL/min) or 1 drop/s (when a microinfusion set is used). Further calculations simply require division by two for the dosage at 30 mL/h (medium dosage) and again for 15 mL/h (low dosage).

This is a nearly ideal method of drug dilution and administration that one can learn and teach to one's colleagues. The "standard" dilutions and delivery rates in Table 1 are presented only for confirmation of the convenience of this method. It should not be necessary to memorize or even retain this table for future reference. Notable exceptions are methohexitol and amrinone.

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Anesthetic Potency and Lipid Solubility

Key Words: POTENCY, ANESTHETIC—MAC. THEORIES OF ANESTHETIC ACTION, LIPID SOLUBILITY. PHYSICS, SOLUBILITY.

To the Editor:

In their recent study Targ et al. (1) found that with isoflurane, substitution of either bromine (making I-537) or fluorine (making I-653) for the 1-ethyl chlorine in this methyl ethyl ether increases or decreases potency (1/MAC) and the oil/gas partition coefficient to the same degree, respectively. Although the oil/gas partition coefficient correlates anesthetic properties and potency surprisingly well, it might be more interesting if the investigators had determined and compared the oil/*water* partition coefficient with anesthetic potency, as biologically relevant partitioning actually involves the aqueous phase (interstitial fluid) and the lipid/protein phase (cell membrane).

Targ et al. (1) also observed that for their oil/gas partition coefficients, the isoflurane series of anesthetics has greater potency than anesthetics such as methoxyflurane, halothane, fluroxene, and cyclopropane. It would be noteworthy if, based on the oil/*water* partitioning, the anesthetic potencies of isoflurane and its homologues were greater than those for other anesthetics. Nevertheless, the discordance between oil/gas partitioning and anesthetic potency among the anesthetics lead the authors to suggest that for any unitary theory of narcosis, the solubility in olive oil does not adequately represent the anesthetic site of action.

This observation is not new and has been made previously for a far broader range of anesthetics by Franks and Lieb (2), who compared anesthetic potency with solvent/water partition coefficients. Franks and Lieb noted that for a wide range of anesthetics, including various chain-length alcohols as well as the noble gases, the correlation between anesthetic potency (1/MAC) and olive oil/water partition coefficient is unsatisfactory. The relationship between anesthetic potency and partition coefficient was even worse for the purely hydrocarbon solvent *n*-hexadecane. Instead, anesthetic potency was found to be proportional to the *n*-octanol/water partition coefficient for a broad range of anesthetic compounds. However, even this correlation may be unsatisfactory for compounds such as acetylene, diethyl ether, and CH_3F. In these compounds, the presence of a polar hydrogen atom(s) substantially increased potency (3). A polar hydrogen is one bonded to a carbon atom to which an electronegative group (e.g., F, O) is also attached. It would be of value to know if the anesthetic potency of the isoflurane family of compounds described by Targ et al. (1), as well as other halogenated anesthetics, can be predicted by the partitioning into a more polar (and protein-like?) compound such as *n*-octanol. In addition, the presence of polar hydrogen(s) may need to be considered in correlating their anesthetic potency with that of other agents.

It appears that an effective "unitary" theory of anesthesia has become increasingly elusive. Nitrous oxide and CF_4 are anomalous and difficult to fit into any systematic correlation of anesthetic properties and potency (3). Furthermore, no unitary theory can explain the agent-specific effects that various anesthetics exhibit, and which may be responsible in part for the cellular and subcellular changes responsible for the anesthetic state.

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In Response:

Dr. Lynch suggests that the correlation of anesthetic potency with the oil/water partition coefficient might be of greater interest than the correlation with the oil/gas partition coefficient because the "biologically relevant partitioning actually involves the aqueous phase (interstitial fluid) and the lipid/protein phase (cell membrane)." Our views do not coincide. The oil/gas partition coefficient is more useful because it relates activity (the gas concentration, which reflects partial pressure or activity) and solution in a suspected locus of action (a hydrophobic phase). Thus, when the gas concentration is fixed at some index of potency (e.g., MAC), the resulting lipid concentration reflects the concentration that would be achieved in a hydrophobic phase during anesthesia. The close correlation between the oil/gas partition coefficient and potency (Table 1) implies that anesthesia is produced by a relatively constant number of molecules dissolved in a hydrophobic phase. This is the "unitary theory" of general anesthesia (which is not really a theory; it simply describes a relationship). Any deviation from the correlation either calls into question the unitary theory or the ability of the solvent used to approximate the suspected locus.

The oil/water partition coefficient provides no similar insight into anesthetic action. The observation that the "biologically relevant partitioning actually involves the aqueous phase (interstitial fluid) and the lipid/protein phase (cell membrane)" is not helpful. The fact that anesthetic passes through interstitial fluid to get to the site of action is irrelevant to the mechanism of action.

The oil/water partition coefficient also is less useful than the oil/gas coefficient because it correlates less well with potency (Table 1). The correlation for the oil/water partition coefficient is so poor that the range of values exceeds a factor of 1000 (compare diethyl ether and CF_4). Even if the value for CF_4 is excluded, there is a 54-fold range of values (see ether and cyclopropane). The most anomalous values are those for anesthetics having either very large water/gas partition coefficients (ether and methoxyflurane) or very small coefficients (CF_4). In contrast to the poor correlation between MAC and the oil/water partition coefficient, the range for the correlation with lipid solubility is less than threefold (compare desflurane and fluroxene).

Finally, despite Dr. Lynch's assertion to the contrary,

Table 1. Correlation of Potency and Solvent Characteristics

Agent	MAC[a]	Oil/gas PC	Product[b]	Oil/water PC[c]	Product[d]
Methoxyflurane	0.22	970	213	226	49.6
Halothane	1.11	224	249	261	289
Isoflurane	1.38	90.8	125	145	200
Enflurane	2.67[e]	96.5	258	128	342
Diethyl ether	3.29[e]	63.2	208	4.98	16.4
Desflurane (I-653)	5.72	18.7	107	79.2	453
Fluroxene	5.99[e]	47.7	286	56.8	340
Cyclopropane	15.9[e]	11.8	188	55.9	889
Nitrous oxide	188[e]	1.40	263	2.98	560
CF_4	2,600[e]	0.073	190	14.6	37,960
Mean ± SD			209 ± 59		4,110 ± 11,900
Mean ± SD (without CF_4)			211 ± 62		349 ± 268

[a] In rats except where noted.
[b] The product of the oil/gas partition coefficient and MAC.
[c] At times I have obtained a water/gas partition coefficient by multiplying the saline/gas partition by 1.05 (1). The oil/water coefficient then is obtained as the ratio of the oil/gas and water/gas coefficients.
[d] The product of the oil/water partition coefficient and MAC.
[e] MAC in dogs. References for the values for MAC and partition coefficients were drawn from several sources (1–11).

nitrous oxide and CF_4 are not anomalous in the context of the correlation of potency and lipid solubility (Table 1). The unitary theory is alive and well, but obviously not living in Virginia.

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Spouse-Controlled Analgesia

Key Words: PAIN, POSTOPERATIVE—patient-controlled analgesia. ANALGESICS, MORPHINE.

To the Editor:

We present a note of caution with respect to a spouse's efforts to improve the quality of postoperative analgesia.

Our patient, a healthy 40-yr-old woman who had undergone lumbar laminectomy, was dissatisfied with the recurrent loss of adequate analgesia that resulted in her repeated awakening after falling asleep. She and her husband decided on a remedy. He would continue to push the button on the patient-controlled analgesia (PCA) device after every lockout interval so she wouldn't get behind. No continuous monitoring such as capnography or oximetry with alarms was used, nor was the staff informed of this plan.

An Abbott Life Care PCA system was used to administer 1 mg/mL of morphine sulfate preoperatively. Each dose was 2 mg, and a lockout interval was set at 10 min. Spouse-activated analgesia was carried out for about 4 h before the plan was discovered by a nurse. The total dose given during this period was not recorded by the nurse discovering the event. The patient could have received up to 12 mg/h by her spouse. At the time of discovery, the patient was sleepy but arousable, with a respiratory rate of 18 breaths/min, heart rate of 106 beats/min, and blood pressure of 108/70 mm Hg.

In addition to the safeguard of the physician writing reasonable dosages and lockout intervals, the patient plays an important role in PCA analgesia in being unable to press the PCA button if too narcotized to do so. Bypassing this safety measure increases the potential for hypoventilation and/or airway obstruction. The present episode occurred in a patient who received preoperative educational teaching and who is herself a registered nurse. The postoperative state may be such that the judgment of patients and their relatives is clouded to such an extent that the staff caring for them must protect them from their own judgments. Educational reinforcement during PCA, closer observation, and possibly some form of continuous monitoring with appropriate alarms (e.g., capnography and/or oximetry) may be indicated in certain patients.

Perhaps future efforts should be directed toward developing systems that would allow only the patient to activate the PCA device. Could a patient's fingerprint be used? In the interim, personnel caring for patients in this setting should be aware that some patients in concert with their relatives/spouses may attempt to achieve higher drug blood levels. Staff must also guard against the potential for attempted murder.

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Intrathecal Alcohol Injection Guided by Electrical Localization of Spinal Roots

Key Words: ANESTHETIC TECHNIQUES, SPINAL—alcohol. ALCOHOL, SUBARACHNOID.

To the Editor:

Chabal et al. (1) recently described the use of electrical stimulation to localize spinal roots before intrathecal alcohol injection for treatment of hip and knee flexion deformities secondary to spasticity caused by spinal stenosis. The report highlights both options for management of spasticity and the increasing need for anesthesiologists' involvement in this clinical area.

The cauda equina consists of a compact array of lumbosacral roots commencing below the conus medullaris (L1-2) that resembles a "horse's tail." The use of percutaneous electrical stimulation during regional anesthesia is well accepted among anesthesiologists, although its utility in the region of the cauda equina has not been established. Of concern is the possibility that despite accurate needle placement in the cauda equina, hypobaric absolute alcohol might migrate from the needle tip and thus increase the extent of neurolysis. Indeed, the injection of intrathecal alcohol below the level of termination of the spinal cord (L2) has been questioned (2).

Hip flexion deformities are produced by sustained hypertonicity or spasticity of two muscle groups, iliopsoas (psoas major and iliacus) and quadriceps femoris (rectus and vasti), whereas knee flexion deformities usually develop secondary to shortening of hamstring muscles. The quadriceps and iliacus muscles are supplied by the femoral nerve whereas the psoas major derives its innervation from the ventral rami of L2-4. I use two different regional anesthetic techniques to decrease hip flexor spasticity, both of which are aimed directly at muscle innervation. Initially, to decrease hypertonicity of the quadriceps and iliacus muscles, the femoral nerve is blocked with 1% etidocaine. If hip flexor hypertonicity decreases, femoral neurolysis with 6% aqueous phenol is performed. Two or even three neurolytic injections may be necessary to produce improvement in hip extension in most cases. A poor response to this technique usually indicates hypertonicity of the psoas major. Recently, Racz et al. (3) published an update on their use of epidural phenol for control of spasticity using a special epidural catheter and daily injections of phenol. I have used this method in two patients with satisfactory long-term results. The technique, which may be termed "epidural radiculysis," allows placement of local anesthetic (diagnostic) or phenol near spinal nerves innervating the psoas major. The sequencing of these interventions is important as the least invasive technique is attempted first and always includes a diagnostic component. In contrast, blockade of the motor innervation of the quadriceps femoris has been largely ineffective in reducing hypertonicity.

There is an increasing trend in spasticity management away from neurodestructive procedures in favor of treatments that preserve motor function and sensation. I have successfully used a temporary (5–8 days) intrathecal infusion of morphine (1 mg/day) in two patients to reduce spasticity after reconstructive plastic surgery on decubitus ulcers (4). Intrathecal baclofen (presently undergoing investigative trials) may be preferable, as it is more potent than morphine and may be titrated to produce predictable spasticity control (5).

I commend Chabal and colleagues for an informative report on subject matter frequently overlooked by anesthesiologists.

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In Response:

Our report on the electrical localization of spinal roots for the injection of alcohol (1) should not be interpreted as a blanket endorsement of this technique for the use in all patients with spasticity. It is well recognized that the complication of bowel or bladder dysfunction after a neurolytic injection parallels the increase in the effectiveness and density of the neurolytic block achieved (2). As the effectiveness of any intraspinal neurolytic block increases, so does the incidence of complications. The injection of intrathecal alcohol is a simple, convenient, inexpensive, and easy-to-administer treatment for spasticity. Alternative sites of neurolytic agent administration, such as the epidural or paravertebral space, can also produce good relief of spasticity. However, they can be technically difficult and time-consuming, and often require multiple injections to achieve the desired result. If, as in our case report, bowel or bladder function is not an issue because of a severe preexisting neurological loss of function, our described technique is useful in assuring that a concentrated dose of neurolytic agent will be injected in close proximity to the stimulated and selected spinal nerves. This method can maximize the effect of agent deposited in the area requiring neurolysis in view of the resistance to neurolytic agents that these patients sometimes display.

We agree that there are a number of medications such as morphine (3), baclofen (4), and possibly α-adrenergic agonists (5) that may be chronically infused directly into the spinal fluid as an alternative method for the treatment of spasticity. The development of these nondestructive reversible treatments holds great promise. However, complicated technology does not come without a cost, be it in terms of infection, mechanical failure, or labor-intensive follow-up visits. How to select appropriate patients with respect to the pathophysiology of the injury or disease remains to be clearly defined. Finally, as the development of tolerance to spinally administered narcotics when used for analgesia has been clearly demonstrated (6), it is possible that with extended therapy, tolerance to infused medications may become a problem in the long-term treatment of spasticity. We agree with Dr. Loubser that the therapy described in our case report may not be appropriate for all patients with spasticity. However, with appropriate selection this technique presents an effective and simple treatment alternative in some patients. In patients in whom bowel, bladder, motor, or sensory function is not a consideration, intrathecal neurolytic therapy remains our preferred treatment, recent advances in technology and pharmacology notwithstanding.

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Obstruction of Venous Return by a Pulmonary Artery Catheter During Cardiopulmonary Bypass

Key Words: ANESTHESIA, CARDIOVASCULAR—pulmonary artery catheterization.

To the Editor:

We would like to report a complication secondary to a pulmonary artery catheter that has not been previously cited in the literature. The patient, an adult, was undergoing two-vessel coronary artery bypass grafting. Before the operation, a triple-lumen balloon-tipped pulmonary artery (PA) catheter was placed in the right internal jugular vein without incident. The balloon was wedged in the PA at 50 cm. After institution of cardiopulmonary bypass, the catheter was pulled back 5 cm as we routinely do to decrease the risk of perforation of the PA. During bypass grafting, the heart was manipulated without problems including anterior rotation for grafting of the right coronary artery. After completion of the grafts, the patient was rewarmed, and normal sinus rhythm returned. It was noted at that time that the tip of the catheter had migrated into the right ventricle. Despite repeated attempts, the catheter could not be passed into the PA. The catheter was therefore pulled back to 20 cm, and passage into the PA was again attempted several times with the balloon inflated. At that time, the perfusionist reported an abrupt loss of venous return to the cardiopulmonary bypass machine. It was then observed that the tip of the catheter with the inflated balloon was visible within the proximal portion of the single venous return cannula that was draining the right atrium. The PA pressure was recorded at negative 40 cm H_2O. Venous return immediately returned to normal after the balloon was deflated. Upon attempting to remove the catheter from the venous return cannula, resistance was encountered. At our request, the surgeon manipulated the catheter within the superior vena cava and right atrium, and the catheter was retrieved from the venous return cannula and placed into the right ventricle. The patient was then weaned from cardiopulmonary bypass successfully while monitoring right ventricular pressures. After this, the PA catheter was advanced without difficulty into the PA.

In conclusion, we experienced a complete obstruction of the venous return during cardiopulmonary bypass when the PA catheter with its balloon inflated was drawn into the lumen of the single venous return cannula. Immediate realization of the cause of the event allowed prompt resolution of bypass flow.

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Further Comments on the Failure of Impulse Propagation in Nerves Marginally Blocked by Local Anesthetic

Key Words: ANESTHETICS, LOCAL—lidocaine, mode of action. NERVE, AXONAL BLOCKADE.

To the Editor:

We appreciate Dr. B. Raymond Fink's thoughtful editorial (1) on our article concerning how the process of impulse conduction is affected when segments of varying length of nerve are exposed to local anesthetic (LA) (2). His comments suggest to us that it would be helpful to clarify two of the issues bearing on this research. Regarding the image of the impulse as it propagates from an unexposed segment to one bathed in anesthetic, we agree with Dr. Fink that it is unlikely that successive nodes along an axon are precisely "identical" in susceptibility to LA. However, our focus was on contradicting the extreme position that LA produces two populations of nodes, blocked and unblocked, and that failure of the impulse occurs when three blocked nodes are encountered in succession. Although this idea has appeared in various guises in several papers dealing with LA block, the image that individual nodes of Ranvier when exposed to increasing concentrations of LA are switched from being fully capable of a regenerative impulse to being incapable of sustaining any action currents is at variance with the fundamental concepts of reversible binding of LA to the thousands of Na^+ channels in a node and with the observed graded reduction of nodal action currents by LA. Thus, the impulse fails at a particular concentration of LA not because it encounters three successive completely blocked nodes, but because the inhibition of ionic channels in all the nodes exposed to that concentration is sufficient to diminish the action currents progressively to the point where propagation ceases. We strongly agree with the point made by Fink in his editorial that conduction safety will vary along the length of an axon, particularly in areas where it branches (see the review by Raymond and Gissen [1987] cited in the paper), but this fact is not in our view the clearest point of departure for understanding conduction failure in peripheral nerve. At marginal blocking concentrations of LA all nodes will show some degree of reduction of ionic currents, and it is quite unlikely that any node will be completely blocked.

The graded action of LA is at the root of the second issue as well. We do not agree with what Dr. Fink called the "well-known fact that CAPs (compound action potentials) as a measure of block are not very reliable." Properly interpreted (accounting for the possibility of temporal dispersion, the nonlinear integration of unit potentials, and the many technical aspects of recording technique) CAP measures are valuable as they give us a parallel look at the way several populations of fibers are affected during an experiment. In our paper we did not intend to criticize Fink and Cairns (3) for *quantitative* errors in their "measurement" of the effects of temporal dispersion. Instead we questioned their *interpretation* of CAPs recorded from a region of nerve that was exposed to LA. Local anesthetic has the effect of reducing the local currents during an impulse and thus diminishing the amplitude of the CAP recorded in the exposed zone, even in the absence of any conduction block or temporal dispersion. Such direct effects were neglected when Fink and Cairns attributed the reduction in CAP amplitude entirely to temporal dispersion on the grounds that the LA concentration was too low to block any fast A-fibers.

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In Response:

I feel sure that many readers will join me in thanking Dr. Raymond and Dr. Strichartz for their comments. The gravamen of my own remarks about CAPs was and remains that CAPs, whether integrated or not, are an unreliable *measure* of conduction block in fiber populations. Neglect of this caveat has led to much past confusion over the differential blocking activity of local anesthetics.

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Flumazenil and Hypoxic Ventilatory Response

Key Words: ANTAGONISTS, MISCELLANEOUS—benzodiazepines, flumazenil. HYPNOTICS, BENZODIAZEPINES—diazepam.

To the Editor:

The recent publication of a paper by Mora and colleagues (1) on the effects of diazepam and flumazenil on hypoxic ventilatory response requires comment.

The authors quantified "hypoxic ventilatory responsiveness" by dividing the change in minute ventilation ($\dot{V}_E$) by the change in arterial oxygen (O_2) saturation. In doing so, absolute magnitudes of $\dot{V}_E$ at each saturation were not reviewed. The authors state that in one patient, the ventilatory response was depressed after diazepam and "even further depressed after flumazenil reversal." Irrespective of the magnitude of the slopes in Figures 2B (sedated) and 2C (postflumazenil), all $\dot{V}_E$ measurements made in this patient were considerably higher at every O_2 saturation after the administration of flumazenil. The minute ventilation at an O_2 saturation of 90% was approximately 41 (baseline), 16 (sedated), and 30 L/min (postflumazenil). Similarly, minute ventilation at an O_2 saturation of 85% was 52, 19, and 39 L/min, respectively. These data thus suggest a partial, but impressive, reversal of respiratory depression, illustrating a shortcoming of choosing the change in minute ventilation with respect to change in O_2 saturation as the sole indicator of hypoxic ventilatory responsiveness. Analysis of absolute $\dot{V}_E$ measurements in all ten patients might better lead to supportable conclusions about the effects of these benzodiazepines on hypoxic respiratory drive under the conditions reported in this study.

These data were obtained from respiratory measurements that were grafted onto a clinical study with different objectives. This explains the large variation in diazepam doses and the durations of sedation reported. This is in contrast to other reports on the effects of benzodiazepines on ventilation in which the dose and timing of benzodiazepine administration and timing of ventilatory measurements were tightly controlled.

We plan to conduct, in the near future, studies specifically designed to measure the effects of flumazenil on ventilatory drive in volunteers after reversal of clinically relevant doses of midazolam. It is our opinion that such studies will lead to more meaningful conclusions about the effects of flumazenil.

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1. Mora CT, Torjman M, White PF. Effects of diazepam and flumazenil on sedation and hypoxic ventilatory response. Anesth Analg 1989;68:473–8.

To the Editor:

In their recent article, Mora et al. (1), suggest that flumazenil may further depress the hypoxic ventilatory drive of patients previously sedated with diazepam. Several limitations in study design and data analysis make these results difficult to interpret.

Mora et al. used an "isocapnic rebreathing technique" to determine hypoxic drive. Although their 6-L rebreathing bag contained 7% CO_2 they state that "normocarbia" was maintained during the hypoxic drive determinations. This is clearly inconsistent: 7% CO_2 (dry) in Philadelphia corresponds to a Pco_2 of approximately 50 (rather than 40) mm Hg (BTPS). Furthermore, the authors do not state whether all hypoxic drive determinations in a given patient were performed at the same CO_2 tension. They imply, instead, that each hypoxic drive determination was performed at the patient's then-current resting CO_2 tension. This may cause significant inconsistencies. For instance, after diazepam, resting CO_2 tension increases (2). If the postdiazepam hypoxic drive determinations were performed at this increased CO_2 tension, the interaction between hypoxic and hypercarbic drive would cause an artifactual increase in the slope of the postdiazepam hypoxic drive; this could account for the authors' inability to document a consistent decrease in hypoxic drive after diazepam. Similarly, if the postflumazenil determinations were performed at lower CO_2 tensions than the postdiazepam determinations (because flumazenil lowered resting CO_2 tension), the postflumazenil hypoxic drive would be artifactually depressed; this could lead to the impression that flumazenil is ineffective in reversing diazepam-induced depression of hypoxic ventilatory drive.

The authors contend that, after diazepam, flumazenil may further depress hypoxic ventilatory drive in some patients. To make this determination, they compared the slopes of the regression lines relating $\dot{V}_E$ to Sao_2 over the "linear portion of the ventilatory response range." From Figure 2 of the original articles (a composite of which is reproduced here as Figure 1), it is apparent that the linear portion of the "postflumazenil" curve (C) is, as the authors contend, less steep than the linear portion of the "sedated" curve (B). However, if the slope is determined from the entire curve, rather than from the arbitrarily chosen "linear portion," it becomes clear that the "postflumazenil" hypoxic drive curve is essentially parallel to the "sedated" curve. Furthermore, the composite figure demonstrates that flumazenil caused ventilation to increase at all oxygen saturations. In this patient, therefore, flumazenil seems to have effectively reversed diazepam-induced depression of hypoxic drive. Failure to recognize this inconsistency resulted from the fact that the authors did not document the displacement (e.g., $\dot{V}_{90}$, the $\dot{V}_E$ at 90% Sao_2) of the hypoxic response curve. Other, similar cases may exist in their patients; unfortunately, the authors have not provided sufficient data to allow the reader to evaluate their results properly.

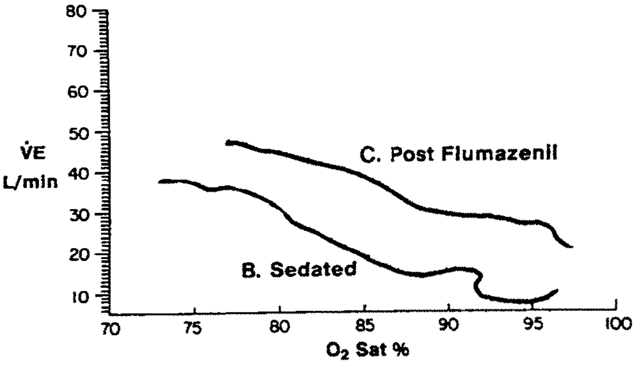

Figure 1. Sedated (B) and postflumazenil (C) hypoxic-drive curves for patient 1 of Mora et al. (1). After flumazenil, ventilation is increased at all values of Sao_2.

Finally, the question of patient safety should be addressed. Specifically, were the sponsor of the study, the Institutional Review Board, and the patients informed that in some cases the diazepam dose would exceed 200 mg, ten times the maximum safe dose indicated on the package insert? The fact that no complications were reported is testimony to the remarkable safety of intravenously administered benzodiazepines.

To summarize, I believe that the study of Mora et al. demonstrates that diazepam significantly depresses hypoxic ventilatory drive (as shown in their Table 3), and that flumazenil effectively reverses diazepam-induced sedation. Limitations in study design and data analysis make it difficult to interpret the effect of flumazenil on hypoxic ventilatory drive after diazepam-induced depression.

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In Response:

We recently reported our findings regarding the effects of diazepam and flumazenil on sedation levels and respiratory (hypoxic) drive in patients undergoing surgical procedures with local anesthesia (1). We concluded that acute tolerance may develop to the respiratory depressant effects of diazepam, and that "flumazenil produces variable effects on hypoxic ventilatory drive when administered after large doses of diazepam." Finally, we suggested that "our preliminary findings indicate the need for further studies to delineate the mechanism of this complex drug interaction."

Dr. Bernstein and Dr. Gross have raised several important points that warrant further clarification. They suggested that we should have measured minute ventilation ($\dot{V}_E$) at an arterial O_2 saturation of 90% ($\dot{V}_{90}$). Although this is a common method for assessing hypoxic drive, we have chosen a different but equally acceptable method for measuring hypoxic drive. Our measurements of hypoxic drive were patterned after the technique originally described by

Rebuck and Campbell (2). Using this methodology, hypoxic ventilatory responsiveness is quantified by dividing the change in $\dot{V}_E$ by the change in arterial O_2 saturation. The measured slope represents the rate of change in $\dot{V}_E$ produced by decreasing arterial O_2 saturations (i.e., a dynamic measurement of respiratory drive). To make accurate measurements of ventilation at specific arterial O_2 saturation values (e.g., $\dot{V}_E$ at an arterial O_2 saturation of 90%), one must achieve a stable measurement of ventilation at a given saturation level. We did not want to present data that we believed could not be easily reproduced using breath-by-breath technology. Using our "dynamic" measure of respiratory drive, flumazenil had variable effects on hypoxic responsiveness after diazepam sedation. It is certainly possible that other measures of respiratory drive (i.e., $\dot{V}_{E90}$ assessments) may yield different results. Although Dr. Gross suggested that we "arbitrarily" chose the linear portion of our hypoxic response curves, in fact the slopes were calculated by a computer using a least-squares regression analysis program that utilized all data points except for baseline (resting) $\dot{V}_E$ values. The R^2 values for the derived curves ranged from 0.92 to 0.98 and attest to the goodness-of-fit of these data.

It would appear that Dr. Gross was somewhat confused by our study design because he stated that our results "suggest that flumazenil may further depress the hypoxic ventilatory drive of patients previously sedated with diazepam." In patients with an average sedation time of 78 ± 14 min, we reported that the average slope of the hypoxic response curve *increased* from 1.3 ± 0.8 to 1.6 ± 0.9 $L \cdot min^{-1} \cdot \% \ O_2 \ sat^{-1}$ after flumazenil (Table 3) (1). However, flumazenil did produce highly variable effects on hypoxic drive after more prolonged exposure to diazepam sedation. In response to his specific criticisms of our methodology, we would point out the following.

First, we primed our rebreathing bag with a mixture of 7% CO_2, 24% O_2, and the balance nitrogen. When this volume percent of CO_2 was introduced from the rebreathing bag into the mechanical dead-space of our circuit (as illustrated in Figure 1) (1), the CO_2 concentration decreased to 6.0–6.5 vol % (43–46 torr) as a result of dilutional effects. More importantly, our technique allows for a breath-by-breath analysis of end-tidal gases (e.g., CO_2 and O_2). Therefore, we are able to rapidly and consistently maintain normocarbia (±1 torr) throughout the entire study period.

Second, we would question Dr. Gross' published method for assessing hypoxic ventilatory drive (3). If one intends to assess the effect of a drug on hypoxic drive, the effects of CO_2 on ventilatory drive should be minimized by maintaining a normocarbic state (2). Gross and his colleagues use a technique that involves increasing CO_2 in each patient (or subject) to 50 torr and then measuring the effects of a drug on hypoxic drive. These investigators may actually be assessing a combination of effects on *both* hypoxic and hypercapnic drive. As the sensitivity of these two mechanisms for stimulating respiratory drive may be unrelated (i.e., subjects may have a very flat response to increasing CO_2 and yet be exquisitely sensitive to the effects of decreasing O_2 tension) (2), one may end up with confusing data regarding the effects of a given drug on hypoxic drive.

The comments by Dr. Gross regarding the administered dose of diazepam indicate a lack of insight into the multicenter protocol design. Patients were maintained at a stable level of sedation (i.e., resting comfortably with their eyes closed but responsive to verbal and/or light tactile stimulation) throughout the procedure to meet the criteria for flumazenil reversal that were established by the sponsor [Hoffman-La Roche]. In the absence of analgesics, even "minor" surgical procedures can be extremely uncomfortable and frequently require high doses of sedative medication (e.g., diazepam). Although this may not be the ideal way to provide perioperative sedation, it was a necessary requirement for this clinical investigation. Finally, the suggestion that we administered doses of diazepam that were "ten times the maximum safe dose" is naive. Given the marked pharmacokinetic and pharmacodynamic variability that exists among surgical patients in their responses to benzodiazepines, most anesthesiologists would *titrate* the drug to a specific clinical endpoint (as we did) rather than simply administer a predetermined dosage based on the manufacturer's package insert!

As a former academic anesthesiologist, we were surprised that Dr. Bernstein would attempt to discredit this study because it was "grafted onto a (multicenter) clinical study with different objectives." By performing our investigation in a clinical setting (as opposed to a "tightly controlled" volunteer study in a pulmonary function laboratory), we believe that these data more accurately reflect the effects of flumazenil when administered to *patients* receiving large doses of diazepam. We strongly support Dr. Bernstein's suggestion that further investigations of the effects of flumazenil on respiratory drive after benzodiazepine-induced sedation are needed. For example, what are the ventilatory effects after flumazenil reversal of benzodiazepine sedation in the presence of opioid analgesia? Many other important questions regarding the clinical use of this exciting new compound remain to be answered.

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Arrhythmia or Dysrhythmia: Let's Standardize Our Nomenclature

Key Words: HEART, ARRHYTHMIAS—semantics. PUBLICATIONS, ANESTHETIC JARGON.

To the Editor:

With rapid advances in medical science, new words and terms are required each year to describe new physiologic techniques and procedures. For example, "pulse oximetry" accurately describes the process by which oxygen saturation is determined by analysis of the pulse of blood in the fingers, toes, or ear lobes. Medical terms that are universally accepted and commonly used with precise meaning should not be discarded in favor of alternate terms unless some clear advantage is gained. Recently, "dysrhythmia" has been suggested as an alternative to "arrhythmia." Arrhythmia has been criticized because it inaccurately connotes to some the same meaning as asystole, that is, no pulse or no heart beat. But does it really?

The ancient Greek meaning of *rhythmos* was "proportion, order or symmetry," and, when prefixed with "a" meant "lack of order or symmetry." H. A. Skinner in his book, *The Origin of Medical Terms,* defines the Greek prefix "a" or "an" before a vowel (the alpha privative), to signify that the term named is deprived of its quality (1). Thus, arrhythmia would mean "deprived of rhythm," "loss of rhythm," and possibly "no rhythm." But all of these terms are different from no pulse or no heart beat. Atrial fibrillation certainly is "deprived of rhythm" or has "no rhythm," but there is a pulse and a heart beat.

Arrhythmia was the chosen term during the era when the first recording and study of the electrical impulse of the heart was performed. A French physician, See, used arrhythmia in 1889 to describe cardiac rhythm disturbances in his publication "Cour et pouls arythmique" (2). In 1903 Wenckebach published his famous monograph "The Arrhythmias," in which he showed that arrhythmias were a type of cardiac irregularity representing a disorder of one of the functional activities of the heart—stimulus production, excitability, contractility, or conductivity (3). In 1908, Sir James MacKenzie, the pioneer of the ink-writing polygraph, used arrhythmia as a general term under which he classified cardiac rhythm irregularities (3). The German physicians Rothberger and Winterberg first described atrial fibrillation in humans and described the electrocardiographic findings of atrial fibrillation in a 1909 paper entitled "Vorhofflimmern und Arhythmia Perpetua" (3). Sir Thomas Lewis, one of the great physicians of his time, who identified the sinus node as the source of the heart beat and related atrial fibrillation to mitral stenosis, also used the word arrhythmia in many of his writings (3).

More recently, an editorial in *Anaesthesia* written by a former editor of the *British Heart Journal* suggested to anesthesiologists in Britain that arrhythmia was the proper term (4). He questioned 300 Greek patients with cardiac rhythm disorders concerning the substitution of dysrhythmia for arrhythmia as acceptable word usage. He wrote: "None thought it appropriate. Such agreement between classical and modern Greek usage, the principles of medical etymology, and the longstanding definition of arrhythmia that had never previously troubled our cardiologic forefathers, persuade me that we should continue to talk of arrhythmia." His final sentence stated: "It would be graceful to see *Anaesthesia* agree that established words are not necessarily wrong ones, and that good reason exists for the preference for arrhythmia as well as a lack of need for dysrhythmia." The editors of *Anaesthesia* agreed. Arrhythmia has been accurately used for centuries to mean "lack of order" or "deprived of rhythm." It, however, does not properly describe "regular" or "rhythmic" tachyarrhythmias, such as atrial flutter and paroxysmal supraventricular tachycardia.

Dysrhythmia apparently first appeared in the medical literature to describe cardiac irregularities in the *British Heart Journal* in 1967 (5). The authors reportedly felt that arrhythmia was unclear and meant "absence of rhythm (pulse)." In *The Origin of Medical Terms,* "dys" is defined as an inseparable adverbial Greek prefix meaning "ill, bad, difficult, painful, or defective"—dysuria, dyspnea, for example (1). Dysrhythmia could, therefore, mean a "bad rhythm" or "defective rhythm." The 26th edition of *Dorland's Illustrated Medical Dictionary* defines the prefix simply as meaning "abnormal," with dysrhythmia defined as a "disturbance of rhythm" generally used to describe an abnormality of speech as in defective breath grouping, dysrhythmia pneumonophrasia; a disturbance of the rhythm of brain waves, cerebral dysrhythmia; and a disturbance of esophageal motility, esophageal dysrhythmia. Thus, *Dorland's* uses dysrhythmia to describe noncardiac rhythm irregularities, and arrhythmia to describe cardiac rhythm irregularities.

Why is this important to anesthesiologists? Unfortunately, our field is the only subspecialty that continues to use dysrhythmia to describe cardiac rhythm disturbances, for cardiologists and cardiology journals use arrhythmia. The World Health Organization and International Society of Cardiology published a special report in 1978 to define the terms related to cardiac rhythm (6). Arrhythmia was chosen as "any cardiac rhythm other than normal sinus rhythm. Such a rhythm may be either of sinus or ectopic origin, and either regular or irregular." The American College of Cardiology's Tenth Bethesda Conference in 1978 also supported the use of arrhythmia (7). In 1981 at an editorial board meeting of the *American Journal of Cardiology,* the use of the word dysrhythmia was discouraged (8). The Index Medicus and the National Library of Congress officially recognize arrhythmia as their official subject heading. And, in our own field, the editor of a recent publication by *Anesthesiology Clinics of North America,* entitled "Diagnosis and Management of Intraoperative Arrhythmias," used arrhythmia consistently throughout the multiauthored text.

Oral and written communication with proper and consistent terminology is important in building respect between subspecialty areas with common clinical and research interests (9,10). In a recent presentation of abstracts at a major anesthesia meeting and in an article in one of our most prestigious journals, the words arrhythmia and dysrhythmia were both used in text, interchangeably. Our specialty of anesthesiology has excellent scientists who devote much time and, in some cases, their entire careers, to the study of cardiac electrophysiology as it pertains to anesthetic practice. If our abstracts, journal articles, and books are to be properly cross-referenced, arrhythmia is the word to use. The editors of *Anaesthesia* have now taken this step by officially recognizing arrhythmia.

Arrhythmia has an accurate meaning, it has been used for centuries, and it remains the chosen word of cardiologic subspecialties. Most physicians are not confused by the concomitant use of the two words, but for some clarity and consistency in communication between cardiologists, surgeons, and anesthesiologists, one word should prevail. We, as anesthesiologists, should follow the guidelines of the cardiologic journals, cardiologic societies, and organizations that have the responsibility of choosing the proper medical terminology, and not abandon the classic "arrhythmia" to describe disturbances of the normal rhythmic beating of the heart.

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On the Water Produced When CO_2 Reacts with Soda Lime

Key Words: CARBON DIOXIDE, ABSORPTION.

To the Editor:

In their recent article on humidification of the Bain and circle systems, Bengston et al. (1) state that 2 moles of water are liberated for each mole of carbon dioxide consumed by soda lime. This is incorrect.

The reactions involving carbon dioxide and soda lime are as follows (2):

1. $CO_2 + H_2O = H_2CO_3$
2. $H_2CO_3 + 2NaOH = Na_2CO_3 + 2H_2O + \text{Heat}$
3. $Na_2CO_3 + Ca(OH)_2 = CaCO_3 + 2NaOH$

Although 2 moles of water are produced in reaction 2, 1 mole was consumed in reaction 1, so that the net protection of water is 1 mole for each mole of carbon dioxide consumed.

This correction in no way affects the results of the study by Bengston et al. It does, however, suggest that less of the moisture required for humidification comes from the reaction of carbon dioxide with the soda lime.

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Does 1 + 1 = 2?—A Continuing Debate

Key Words: POTENCY, ANESTHETIC—nitrous oxide, enflurane. INTERACTIONS (DRUG)—nitrous oxide, enflurane.

To the Editor:

In the following essay we continue our debate regarding the anesthetic relationship of nitrous oxide and volatile anesthetics (1,2). In an experiment evaluating the anesthetic additivity of enflurane and nitrous oxide in rats, Cole et al. (1) observed a nonlinear relationship in the ability of nitrous oxide to decrease the MAC requirement of enflurane. In an accompanying editorial Eger (2) addressed several salient points regarding the authenticity and clinical relevance of this finding.

Our first issue regards the significance of nonlinearity to the unitary theory of narcosis. Eger believes that inhalational anesthetics (as assessed by MAC) effect an anesthetic state by a common mechanism (unitary theory) such that 0.5 MAC of anesthetic A and 0.5 MAC of anesthetic B should add to 1.0 MAC. We all agree that this has been widely supported by clinical experience, and that it should be true if the unitary theory of anesthesia is correct and not modified by extraneous factors. However, Cole and coworkers believe that their data are not compatible with the prediction that increasing the concentration of nitrous oxide results in a linear decrease in the requirement of enflurane to produce 1.0 MAC. This may be inconsistent with a unitary theory of anesthesia; however, it might also be argued that dose-dependent modulations of anesthesia or analgesia occur with nitrous oxide alone, for various volatile anesthetics, or as an interaction between nitrous oxide and volatile anesthetics. Such an argument would allow for a modified unitary theory.

Second, we agree that the entire dose-response curve does not have to be defined to question linearity. If the deviation in the original dose-response curve is correct (1), it argues against linear additivity regardless of the remainder of the curve. One of us (Dr. Eger) is not convinced that a deviation exists: examination of Figure 1 from the original paper suggests a discontinuity in the data, with 30% nitrous oxide exerting a greater anesthetic effect than 60%; similarly, 70% and 80% bear an inconstant relationship to each other in that figure (1). Cole et al., although confident of the original data, remain unsure of its relevance: even if correct, the attack on the unitary theory would be trivial if the deviation from linearity were minor. The extrapolation in Figure 2 of the original paper implies a major deviation. However, if nitrous oxide MAC exceeds 2 atm, the deviation is that of the 30% nitrous oxide point and becomes minor.

Third, all parties have reservations concerning dose-response curves constructed from a limited number of observations and diverse sources (3–5). Beyond the quality of work provided by each investigator, the accuracy of a dose-response curve based on data from different laboratories depends on the objectivity of the measurement made and its potential variability. A small variability in each data point increases the likelihood that a composite dose-response curve is accurate. Thus, studies documenting linear additivity for the enflurane-nitrous oxide dose-response curve in the human (3–5) must be viewed with far more caution than studies (such as that presented by Cole et al. [1]) from a single laboratory.

Fourth, Cole et al. object to the exclusion of the 30% nitrous oxide data by Eger (2) and argue that a scientific theory should be compatible with all legitimate data. Although Eger concedes this point, he reiterates the arguments made in the third paragraph (i.e., that the importance of the 30% point is in the extent to which it deviates from linear additivity).

Finally, results from additional studies performed by Cole and associates (6) support the nonlinear argument. Whereas any technical error present in the first study may have been duplicated, such an error is not apparent to either Cole et al. or Eger. However, even if the data from both studies are correct, they point to but a minor flaw in the unitary theory. That is, there may be a common mechanism by which the inhaled anesthetics act, but this action may be modestly altered by side effects of particular agents. For example, some agents may evoke an increase in sympathetic activity at certain partial pressure ranges, and such increased activity may increase anesthetic requirements. We agree that further studies testing the extent to which the theory of additivity is compromised must include an evaluation of the entire dose-response curve.

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Problems with Eye Opening After Propofol Anesthesia

Key Words: ANESTHETICS, INTRAVENOUS—propofol.

To the Editor:

It has been suggested that intravenous anesthesia may, especially if it includes propofol, be associated with clear and rapid recovery even after long anesthesia. This might not always be quite the case.

Six of 50 consecutive patients scheduled for ear, nose, and throat procedures using a standardized total intravenous technique with oxygen-enriched air, propofol infusion, fentanyl, and atracurium showed postoperatively an inability to open their eyes either spontaneously or in response to verbal commands. This phenomenon lasted between 3 and 20 min after the end of the anesthetic and after return of normal muscular power (50 Hz tetanus for more than 5 s, headlift for at least 5 s, articulate speech, and sustained handgrip). All six patients were well oriented in space and time.

Three of the six patients opened their eyes by using one of their fingers. One patient complained about not being able to open his eyes and asked for relief of this symptom; another patient stated that he felt his eyes were loaded with

50 kg of lead. Three patients were examined further. Two of the three patients initially showed a complete loss of ocular motility.

A residual effect of atracurium on the sensitive musculature controlling eye movements is an unlikely explanation because scores for eye opening comparable to the ones shown by our patients are associated with an inability to lift the head, a weak squeeze of the hand, or a significantly reduced tidal volume (1). We think propofol is likely to be involved in this transient myastheniclike weakness. There are many reports on postoperative sequelae of propofol anesthesia, including hallucinations (2), patients making amorous advances (3), muscular imbalance (4), and muscular hypotonus (5). To our knowledge the inability to open the eyes after propofol anesthesia has not yet been described (ICI Pharmaceutical Information Service, personal communication). This phenomenon is at present under further investigation.

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New Needle for Combined Epidural and Spinal Techniques

Key Words: EQUIPMENT, NEEDLES—spinal, epidural.

To the Editor:

It recently came to our attention that Campbell noted in an editorial the potential for overcoming some of the limitations of conventional spinal or epidural anesthesia and analgesia by use of our E-SP MultiPurpose Epidural Spinal Needle (1). This recently patented device was indeed designed with the intent to facilitate combined spinal and epidural anesthetic techniques, principally but not exclusively, for obstetrical and related surgical pain relief. It is the first patented dual-cannula regional anesthetic needle designed for just this purpose. We write to clarify the regulatory status of the device as such a prominent reference has prompted several inquiries into purchasing the needle. Currently, the needle is the subject of a clinical trial under an Investigational Device Exemption. We hope to obtain Food & Drug Administration approval to market the device in the United States and certain countries abroad. At present, neither the device, nor related accessories are commercially available. This should help to clear up any confusion arising from Campbell's excellent editorial comments.

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Book Reviews

Neurosurgical and Medical Management of Pain: Trigeminal Neuralgia, Chronic Pain and Cancer Pain

Ronald Brisman, ed., Boston: Kluwer Academic Publishers, 1989, 205 pp, $79.95.

This book is a concise resource detailing various neurosurgical options in the treatment of trigeminal neuralgia, chronic noncancer pain, and cancer pain. Dr. Brisman has edited the volume based on the spectrum of patients seen in his 12-yr experience from 1975 through 1987 and his review of the work of many others.

The chapter dealing with the anatomy and physiology of the pain system by Dr. Robert Goodman is one of the most readable and informative discussions of the recent information in this area that this reviewer has found. Throughout the chapter, Goodman describes in clear detail the various characteristics of the nociceptive fibers, their associated neurotransmitters, the spinal cord tract organization, supraspinal pain pathways, and descending modulatory systems.

The section on treatment of trigeminal neuralgia, although complete, is heavily weighted to the various surgical approaches. For the general algologist, this section contains many useful insights but they tend to be buried in the extensive discussion of the surgical experience.

Unfortunately, the section on management of chronic, benign pain by anesthesiologists falls short. The lack of recognition of stimulation-produced analgetic responses (SPA responses) and their role in placebo injections or trigger point injections, confusion over the afferent nociceptive system running with the efferent sympathetics, and the lack of demonstrated efficacy of *any* treatment in the final, overall rate of long-term postherpetic neuralgia are particular problem areas.

The remaining chapters are useful overviews; the section on spinal cord stimulation is particularly good. This reviewer would certainly reinforce Brisman's summary statement that ". . . spinal-cord epidural stimulation is the neurosurgical procedure of choice for most patients with chronic noncancer pain that remains intractable and agonizing in spite of conservative forms of treatment." Notable for its absence is any discussion of the surgical treatment of biomechanical spinal pain.

This book is a useful resource that complements another recent publication by Gybels and Sweet on the neurosurgical approaches to the treatment of pain. For the non-neurosurgeon algologist, Brisman's publication has the advantage of being fairly readable and of providing a thorough review of the neurosurgical treatment of facial pain particularly, but at $79.95 is somewhat overpriced.

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Autologous Blood Transfusion: Current Issues

R. L. Thurer and L. Maffei, eds., Arlington, Va.: American Association of Blood Banks, 1988, 260 pp, $24.00.

If no transfusion is the safest transfusion, than autologous blood transfusion is certainly the second safest. *Autologous Blood Transfusion: Current Issues* contains the papers and recorded panel discussions of a conference sponsored by the National Autologous Blood Resource Center in May 1988. The participants in the conference read like a "Who's Who of Autologous Blood Transfusion and Blood Conservation" and cover all aspects of autologous blood transfusion from use in special circumstances such as pregnancy and cardiac surgery to "speculative deposits" (i.e., the donation of one's blood for possible future use at some undetermined date) and crossover autologous blood (i.e., the transfusion of blood collected from potential autologous donors to other patients after there is no longer possible need for the donor's use) as well as, in this era of cost containment, the cost and charges associated with autologous blood transfusion.

Between 1982 and 1987 there was a 15-fold increase in units collected preoperatively (18,000–290,000) according to an American Association of Blood Banks survey, attesting to the explosive growth in the acceptance of the concept of using one's own blood by patients and their physicians alike. This growth is undoubtedly related to the recognition that AIDS can be transmitted by blood transfusion (but non-A, non-B hepatitis remains a much greater risk).

Panel discussion recordings add much to conference proceedings such as these and provide answers to questions that those of us who did not attend the conference might have asked. Additionally, they raise controversial issues. For example, is acute normovolemic hemodilution a technique to be used or should the patient just be left with a lower hematocrit? Although the discussions did not offer definitive answers to such questions, they did help define

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the issues. One disconcerting aspect of the panel discussion recordings was reference to papers apparently presented orally at the conference, but not contained in the proceedings.

In summary, this economically priced paperback monograph concisely and completely covers autologous blood transfusion in all its variations and will be of use to all participating in the administration of blood products to patients. Perhaps it will be of most value in centers where the acceptance of the concept of autologous blood transfusion has not shown the explosive growth the statistics quoted above reflect. If some of these centers were to increase the use of autologous blood on the basis of this conference and monograph, the efforts that went into both would indeed be justified.

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Drug Treatment of Cancer Pain in a Drug Oriented Society

Volume 11, Advances in Pain Research and Therapy
C. Stratton Hill, Jr. and William S. Fields, eds., New York: Raven Press, 1989, 380 pp, $86.00.

This monograph, which is a compilation of proceedings from a conference organized by the University of Texas, M.D. Anderson Cancer Center in March 1988, examines factors external to medical knowledge that influence our approach to the management of cancer pain. The papers are derived from a uniquely diverse group of specialists, including basic scientists, psychologists, sociologists, historians, attorneys, philosophers, and anesthesiologists, among others. Cultural, historical, and legal perspectives are explored as well as more pragmatic issues of recent advances in basic opiate pharmacology and physiology. The editors hope that by addressing these fundamental concepts a fuller appreciation of our attitudes toward opiates and, therefore, a more logical approach to their utilization will be gained. In general, this volume accomplishes its goal.

The text is divided into six subsections. The introductory discussion succinctly outlines the major issues that are hypothesized to influence the treatment of cancer pain. These include professional and lay misconceptions of opiate addiction, changing cultural perceptors of pain, regulatory pressures, and concerns of illicit diversion of legitimate pharmaceuticals.

The second section is a cohesive, well-focused, and comprehensive synopsis of these cultural, legal, and ethical dilemmas. The papers are well written, interesting, and avoid the rhetorical style common in many ethical dissertations. Most importantly, they offer useful pragmatic insights and potential solutions germane to the topics discussed. Particularly outstanding is Johnson's discussion relating the genesis of contemporary cultural attitudes of pain with the historical development of effective analgesics. The subsequent conflicts with traditional Judeo-Christian values are felt potentially to influence therapeutic decision making.

Unfortunately, in the next two sections, organization is lacking and frequently, large portions of the papers are devoted to generic recapitulations of broader concepts more eloquently covered in preceding works. The material often tends to be random, and somewhat oblique to the underlying topic of the text. As an example, the discussion on pain control in narcotic-dependent patients pertains more to methods of acute pain management and is less relevant to the more persistent pain of cancer patients. One may also take exception to the statement that amitryptyline is frequently abused and offers little value in this group of patients, inasmuch as this is not the common clinical experience (Clin Neuropharmacol 1983;6:271–95). In Hode's chapter, the author confuses issues of drug compliance with efficacy and advocates patient education to improve compliance despite presenting data that are contradictory to his hypothesis. The discussion of pharmacologic misinterpretation is far too rudimentary and its contents are better addressed in other sections. Houde's comment concerning "around-the-clock" administration of analgesics as "neither wise nor safe in patients who cannot be closely monitored" is surprising in that clinical experience suggests the contrary (N Engl J Med 1985;313:84–95). Fortunately, several important contributions do appear. Jaffe's discussion of opiate-induced euphoria presents compelling arguments for the beneficial effects of euphoria in reducing the suffering of cancer patients.

The influence of governmental regulatory pressures is examined in the next section. These selections are well integrated and are easily read. Potential legal impediments to legitimate opiate utilization are discussed and several viable alternatives are presented.

The concluding section of the text contains several excellent contributions. Knapp et al. present a complete and well-referenced review of opiate receptor pharmacology. The following discussion by Yaksh et al. of the spinal modulation of pain complements the chapter of Knapp et al. effectively and is an efficient introduction to a complex subject. The chapter concerning novel routes of opiate administration is generally complete; however, the impression that patient-controlled analgesia cannot be delivered continuously is outdated, as several ambulatory devices are available that offer this option. The lack of a specific discussion concerning adjuvant analgesic therapy is a surprising omission from this text.

In summary, this monograph provides a unique collection which comprehensively addresses societal factors that directly impact on therapeutic decisions in the patient with cancer pain and would be best utilized as a library reference source.

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A Guide for Authors

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2. *Personal author(s) books and monographs*
   Eisen HN. Immunology: an introduction to molecular and cellular principles of the immune response. 5th ed. New York: Harper and Row, 1974:406.
3. *Chapter in a book*
   Weinstein L, Swartz, NM. Pathogenic properties of invading microorganisms. In: Sodeman WA, Jr, Sodeman WA, eds. Pathologic physiology: mechanisms of disease. Philadelphia: WB Saunders, 1974:457–72.

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Editorial

Observational Studies and Predictive Models

L. Richard Smith, PhD

Key Words: STATISTICS.

The paper by Shah and colleagues (hereafter referred to as Shah), "Angina and Other Risk Factors in Patients With Cardiac Diseases Undergoing Noncardiac Operations" (1), is an important study because of the prevalence of cardiac patients that require noncardiac surgery. It is also important because it is a paradigm of a number of studies that have appeared in the literature recently (e.g., 2,3). Statistical analysis plays a central role in these studies. The purpose of this editorial is to use Shah's study as a point of departure to expand on the statistical methodology and suggest some other methodologies for future investigations. This editorial will concentrate on the design of these studies, patient selection, variable selection, statistical model selection and evaluation, and interpretation of results. The principles and pitfalls of the statistical methodology are crucial in evaluating these epidemiologic studies.

There are two classes of observational studies in the clinical setting, retrospective and prospective. In retrospective studies, past patient records are reviewed to collect the relevant prognostic and outcome variables. In prospective studies the relevant prognostic and outcome variables are collected from patients as they are treated and followed.

Retrospective studies are generally quicker and cheaper to conduct because patients have already been treated and the data collected. There are, however, several problems with retrospective studies. Among them are the following: patient records may be lost; definition of the variables may have changed over the time period of the study; and data required for assessing outcome may be missing. Furthermore, these problems may be related to the type of surgery or seriousness of the patient's illness, thus creating serious biases in the results. If a patient has any one of the prognostic variables missing, that patient drops out of any analysis in which the variable is missing. This reduces the sample size and hence reduces the power of the model to predict outcomes.

Prospective studies, on the other hand, take longer to conduct and thus are more expensive. But with careful design, prospective studies permit unbiased patient selection (reducing the likelihood of overlooking patients) and consistent observation and data collection for the length of the study.

Shah chose to study prospectively 688 consecutive cardiac or elderly (>70 yr) patients undergoing various noncardiac surgeries. Twenty-four prognostic variables and two adverse outcome variables were collected. Complete data were collected on all patients. The prognostic variables were analyzed to determine which subset of them was predictive of an adverse outcome, perioperative myocardial infarction (PMI) and/or cardiac death during the hospitalization.

When one goal of the study is to determine the relative risk of adverse outcomes in two or more groups of patients, it is important that patients be stratified into groups that are relatively homogeneous with respect to procedure. Shah classified patients into three groups based on surgical procedure: thoracic and abdominal, aortic or other peripheral vascular disease, and an "all other" group. An "all other" group may be so heterogeneous with regard to risk that any effect will be diluted. If the "all other" group is not at significantly higher or lower risk than the well-defined groups, it can be difficult to generalize from the results. This can be circumvented by

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including in the analysis only those groups that are well defined.

In any clinical study, variable selection is very important. Two sets of variables are required to be defined: the outcome variables and those variables known as prognostic variables which may predict outcome variables. All variables should have commonly understood definitions with conventional meanings, with minimal room for interpretation by the observers or data collectors. The greater the accuracy in assessing the variables, the greater the predictive power of the model, and the fewer the number of patients required to achieve meaningful results. For example, Shah has defined PMI explicitly and narrowly as an increase of serum CK-MB isoenzyme levels with the presence of at least one of two other criteria: chest pain or electrocardiographic evidence of subendocardial or transmural myocardial infarction. An independent confirmation of PMI by a cardiologist not directly involved with the patient or the study was required. Cardiac death was defined as death after PMI, after documented cardiac dysrhythmia or cardiogenic shock, or when death was sudden and unexplained. Either PMI or cardiac death, or both, constituted the adverse outcome for the study. Thus, the outcome variables are well defined and easily understood. The prognostic variables are similarly well defined.

Among the prognostic variables, two types are of interest: those that cannot be altered but can be used for improved patient selection (e.g., age, prior myocardial infarction), or those that can be altered to reduce risk (e.g., hematocrit, blood pressure). For surgical studies, prognostic variables represent the patient's condition before surgery or represent those factors that are determined before surgery, such as anesthetic or surgical technique. This precludes the use of variables occurring after the beginning of surgery. Variables such as length of time in surgery or episodes of hypotension during surgery are outcome variables. For example, even though perioperative hypotension may be strongly associated with adverse outcomes (indeed, it is an adverse outcome itself), it cannot be used as a selection criterion for surgery nor can it be altered until it occurs—after surgery begins. Whatever underlying physiologic process causes perioperative hypotension may also predispose the patient to PMI or cardiac death. Shah has clearly used the preoperative variables only, although he alludes to measuring and analyzing the correlations of some intraoperative factors with adverse outcome.

There is a tendency to collect as many variables as possible, analyzing all of them with regard to the outcome variables, hoping not to miss any important prognostic factor. There is a limit, however, to the number of variables that can be effectively analyzed jointly. Harrell et al. (4) suggested approximately one variable for every 10 observations in the least frequent category of outcome variable. With the 40 adverse outcomes in Shah's study, this rule of thumb would suggest that only four variables could be jointly evaluated effectively. To analyze 24 variables and keep the 10-to-1 ratio would require 240 adverse outcomes for the predictive model to be trustworthy. By fitting many variables to few outcomes, there is a likelihood of an unreliable model—a model that results in inaccurate predictions on an independent patient sample.

There are several ways to avoid the problem of too many variables. One common method is to analyze each prognostic variable separately for its influence on outcome, then use only those variables that are "significant" at some predetermined level. This technique raises a multiple comparison problem. The likelihood of finding spuriously significant factors is increased when many variables are examined. In addition, very often several of the significant variables will be highly correlated, and, when they all are included in the model, only one or two will be significant. Another serious problem with this technique is that some important prognostic variables may be overlooked. Variables that are not significant by themselves may become significant in combination with other variables.

Another approach centers on collapsing groups of like variables into one index. Gersh et al. (5), in analyzing the effect of coronary bypass surgery on patients over the age of 65 yr, collapsed several associated disease variables into one variable by simply counting the number of associated diseases. Similarly, Hickey et al. (6) summed the number of each patient's comorbid disorders in a group of patients undergoing treatment for ischemic mitral regurgitation. In both studies, these count variables proved to be important prognostic factors. Califf et al. (7) produced a strong predictor of adverse outcomes by grouping anginal characteristics into a single angina score, and Harrell et al. (8) showed how 30 original variables could be reduced to 10 entities by linear combinations of like variables. Increased use of such indices that *do not use the outcome data* can reduce the number of prognostic variables and avoid the problem of model instability.

How an individual variable is represented in the model is also of importance. Continuous variables, such as age, are often dichotomized into two ranges for ease of explication. This often masks important effects. In Shah's study, age is dichotomized into two groups: <70 yr and ≥70 yr. This assumes that the risk is constant for every age up to the age of 70 yr, whereupon the risk jumps to a higher level and is constant thereafter. By including age as a continuous variable, an incremental risk could be estimated for any age increment, thus improving the predictive power of the model. Even this may not be sufficient. There is evidence that increasing age increases risk of adverse outcomes at a fixed rate up to (approximately) age 65 yr, after which there is a dramatic increase in the incremental risk for an increase in age. New techniques (9) have been recently developed to model such nonlinear effects of the prognostic variables using splines or segmented polynomials.

Model selection for analysis of binary outcomes is of primary importance. There are two candidate statistical models for this analysis: the linear discriminant function (LDF) and the logistic regression model (LRM). Both the LDF and the LRM classify patients based on a linear combination of the prognostic factors, $a_0 + a_1x_1 + \ldots + a_nx_n$. The a_i are coefficients to be estimated, and the x_i are the prognostic variables. If an individual a_i is significantly different from zero, we conclude that the corresponding variable is a significant factor. The LDF, which is a linear regression model for classification, is a very powerful tool when the assumption of jointly normally distributed prognostic variables holds. When this multivariate normality does not hold, such as when the prognostic variables are dichotomized, the results can be biased. The LRM considers P to be the probability of being classified in the adverse outcome group and assumes that $\log(P/1 - P)$ is a linear combination of the covariates. The LRM model makes no assumptions about joint multivariate normality. It produces a probability from 0 to 1 of the outcome. Harrell and Lee (10) made a study of the LDF and LRM and concluded that the LRM was very nearly as good as the LDF when multivariate normality holds and that the LRM is superior to the LDF when multivariate normality is not achieved. A further reason for use of the logistic regression model is the ease of interpreting the coefficients. Shah gives a nice explication of this in Table 3. Shah has chosen the logistic regression for the correct reasons: that multivariate normality is violated and would introduce unknown biases into the LDF analysis, and that the LRM lends itself to ease of interpretation. Hosmer and Lemeshow (11) provide an excellent overview of this subject. The LRM is the model of choice here, as it is in most studies involving acute outcomes.

Shah has also taken the necessary step of testing the adequacy of the model. Using the prognostic variables found from the model based on the entire population, the model was refitted on half the data (the observation sample). These new parameter estimates were then used to estimate the probability of adverse outcome for each of the patients in the second half of the data (the holdout sample), and predictions were compared with observed outcomes. The holdout sample is not a truly independent test because the selection of variables was based on the entire study population, which includes the holdout sample. It would be interesting to know how the values of the parameter estimates and their standard deviations changed from the model based on the entire sample of 688 patients to the model based on the observation sample with 336 patients. These changes could shed some light on the stability of the model. For instance, if the coefficient for a prognostic variable changes sign, or its magnitude changes dramatically, this could signal some model instability. Shah plots the probability of adverse outcome versus case number for those patients in the holdout group who had an adverse outcome and for those who did not. The median probability for the adverse-outcome group is 0.09 and for the no-adverse-outcome group is 0.02. The model predicts higher probabilities of adverse outcome for the adverse-outcome group, but more information is needed about the predictive accuracy of the model. Perhaps the simplest information to provide is the sensitivity and specificity for the model. The sensitivity of a test is the proportion of patients with adverse outcomes that are predicted to have adverse outcomes. The specificity is the proportion of patients free of adverse outcomes that are predicted to be free of adverse outcomes. The sensitivity and specificity are dependent on the probability level at which discrimination is to occur. If this probability level is arbitrarily set to 0.50 for testing model adequacy, one infers from Shah's plot that the model has low sensitivity because so few patients in the adverse-outcome group have a probability of adverse outcome greater than 0.50. Sensitivity and specificity, however, have their own problems. Two patients with probabilities of adverse outcomes of 0.49 and 0.51 would be classified into groups 0 and 1 respectively, even though they are very similar in risk.

Of course, the 0.50 discrimination level for model evaluation may not be the point at which a clinician makes a decision about a patient. Depending on the risk to the patient of not having surgery, the clinician may choose a higher or lower discrimination level. A more comprehensive measure of model adequacy is required. If the discrimination level is varied from 0 to 1 and the sensitivity and specificity calculated at each point, the receiver operating characteristic curve (12) can be constructed by plotting the sensitivity versus 1 − specificity. The area under the receiver operating characteristic curve is a powerful measure of predictive discrimination. It is the probability that in randomly selected pairs of patients where one patient has an adverse outcome and the other does not, the patient with the adverse outcome is the one with the higher predicted probability. This measure provides a single number for the model's discrimination ability. A direct comparison of the discriminatory power of two different models can be made by statistically comparing the areas under the receiver operating characteristic curves.

Finally, the model's predictive reliability should be validated on the scale of absolute predicted risk. One way this can be done is by comparing each quintile of risk with the observed prevalence in the quintile. Large differences between observed and predicted risks would indicate an unreliable model. Because the use of the LDF and LRM has become common in anesthesiology clinical studies, there needs to be a consistent standard for reporting and testing the adequacy of predictive models.

In the model used by Shah, all the prognostic variables are dichotomized into 0 or 1, depending on whether the variable is present in the patient. The base, or reference, model, with all prognostic factors set to zero, represents the probability of an adverse outcome for a patient in the "all other" group who has no other risk factors. Inferences beyond the range of the data should be made with care, however. For example, if a 1 is substituted for each of the definitive surgical groups, with all other factors being 0, this would describe a patient with no risk factors having two different kinds of surgery. In this case, the probability of adverse outcome is 0.03 (3%). There is some danger in too literal an interpretation here. No patients in the study had two or more kinds of surgery, although the model allows for such a circumstance.

In presenting the results from the analyses, Shah includes an estimate of each effect, standard deviation of the estimate, significance levels, and the estimated probability of adverse outcome for the specific factor when considered alone. Presentation of the parameter estimates (rather than just P values) is important because it allows the reader to judge the magnitude and direction of the effect. It is interesting that Shah has not slavishly adhered to the "$P < 0.05$" rule for including factors in the model. There may well be cases in which factors with P values greater than such an arbitrary cut-off should be included. The groups may have small differences in important prognostic factors, none of which would be individually "significant." The cumulative effect, however, could be important. Furthermore, including a factor known to be important may change the estimate or variance of the coefficient of another factor. Choice of the "nonsignificant" factors for inclusion depends on both the investigator's knowledge of the physiological process and the interrelationships among all the prognostic factors.

This study has provided useful insights into the processes leading to adverse outcomes for cardiac patients undergoing noncardiac surgery. The results of the analysis have identified factors that appear to influence adverse outcome but may not be strongly predictive. Before a model is put to clinical use, however, it should be tested on an independent sample, preferably at another institution. Multiinstitutional studies would provide a mechanism for developing and testing these complex models.

The basic tenets of prospective patient recruitment, variable selection and definition, choice of statistical model, and assessment of model adequacy are necessary requirements for clinical studies. The role of the statistician in these studies is as a coinvestigator who must be involved at every step of the study. Beginning with experimental design, the statistician can provide estimates of sample size based on the estimated adverse outcome proportion, the number of prognostic variables which may be analyzed effectively, and the magnitude of prognostic variable effects. The choice of model is of critical concern. Incorrect model choice may yield biased estimates of the prognostic variables effect, or perhaps incorrectly identify significant prognostic variables. Assessment of model adequacy provides the reader with the information required to judge whether the model is robust enough to be used in other institutions or studies. Finally, because of the important roles of statistics in these studies, consistent editorial policies regarding statistical review of manuscripts need to be developed and applied.

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1990;70:240–7

Angina and Other Risk Factors in Patients With Cardiac Diseases Undergoing Noncardiac Operations

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H. Kurt Jacobs, PhD, Katherine Mestan, BSN, RN, and Martha Schaafsma, BSN, RN

SHAH KB, KLEINMAN BS, RAO TLK, JACOBS HK, MESTAN K, SCHAAFSMA M. Angina and other risk factors in patients with cardiac diseases undergoing noncardiac operations. Anesth Analg 1990;70:240–7.

Six hundred eighty-eight consecutive patients with cardiac diseases or who were older than 70 yr of age, all of whom were undergoing noncardiac operations, were studied. Twenty-four preoperative risk factors were analyzed for the outcome of perioperative myocardial infarction (PMI) or cardiac death using stepwise logistic regression. Old age, emergency operation, angina, previous myocardial infarction, electrocardiographic signs of ischemia, type of surgical procedure, and hypokalemia were identified as individual factors useful in predicting outcome. Thirty-two patients (4.65%) developed PMI. Seven of these 32 patients (21.9%) and eight more patients without PMI—a total of 15 patients (2.2%)—died a cardiac death. Nonfatal but serious complications occurred in 23% of the patients. Patients undergoing emergency operations and patients with chronic stable angina, previous myocardial infarction, and electrocardiographic signs of ischemia were found to be at increased risk for PMI and cardiac death.

Key Words: HEART, ISCHEMIA—operative risk. RISK, PERIOPERATIVE—angina.

Noncardiac operations performed on patients with ischemic heart disease are increasingly frequent. Various studies have found a correlation between the preoperative history of myocardial infarction (MI) less than 6 mo old and the incidence of a perioperative myocardial infarction (PMI) (1–4). However, the relationship between chronic stable angina or electrocardiographic (ECG) signs of ischemia and the incidence of PMI is not known. This prospective clinical investigation was undertaken to study the incidence of PMI and cardiac death in patients with a preoperative history of cardiac disease undergoing noncardiac operations and to identify the preoperative risk factors that might help to predict these adverse outcomes.

Materials and Methods

Six hundred eighty-eight consecutive patients with cardiac diseases or who were older than 70 yr of age, all of whom presented for noncardiac operations, were prospectively studied over a period of 18 mo. Preoperative and intraoperative data were collected by a participating staff anesthesiologist. The preoperative information included demographics, medical and cardiac history, findings of detailed physical examinations performed by a staff anesthesiologist, hematocrit, blood urea nitrogen, serum creatinine and electrolytes, liver enzymes, findings of chest radiograph, and 12-lead electrocardiogram with a rhythm strip. Intraoperative data obtained included the types of monitoring, anesthetic technique, anesthetic drugs, support of cardiovascular system with the use of vasopressors, ionotropics, or vasodilators, and intraoperative complications including tachycardia, hypotension, hypertension, and ST-T changes. Pulmonary artery occlusion pressures were recorded in patients in whom a pulmonary artery catheter was inserted. Intraoperative data were recorded on a separate data sheet by a resident anesthesiologist or a nurse anesthetist involved in the case. The clinical management of the patients was left at the discretion of the anesthesiologist. The patients' daily courses

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This study was performed at Loyola University Medical Center, Stritch School of Medicine, Maywood, Illinois, approved by the Institutional Review Board for Protection of Human Subjects, and was funded by the Department of Anesthesiology, Loyola University Medical Center, Maywood, Illinois.

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were followed during the entire hospital stay. All of the 688 charts, including the anesthetic record, were reviewed by one of the participating physicians after the discharge or death of the patient, so as to record data on intraoperative as well as postoperative complications.

Unstable angina was defined as the presence of one of the following: (a) recent onset of effort angina (within 1 mo), (b) increasing severity or frequency of previously stable angina, and (c) angina at rest. Electrocardiographic signs of ischemia were defined as depression of ST segment of ≥ 1 mm and/or inversion of T wave in the immediate preoperative 12-lead electrocardiogram, in the absence of digitalis, left-ventricular hypertrophy, hypokalemia (serum potassium <3.5 mEq/L), or ventricular conduction abnormality. If any patient was suspected of having congestive heart failure or if any murmur other than soft systolic flow murmur was heard on physical examination, he or she was referred to the cardiology service for further evaluation. Important valvular diseases such as aortic stenosis were included as a characteristic only when the diagnosis was made by a cardiologist. Diagnostic cardiac catheterization or echocardiography was performed in some patients when it was clinically indicated. Atrial dysrhythmias were diagnosed if premature atrial beats, atrial flutter, or fibrillation was present on any of the preoperative electrocardiograms in the medical charts. Similarly, the charts were reviewed for quantification of premature ventricular contractions, and ventricular dysrhythmia was included as a characteristic when a patient had more than five premature beats per minute or a past history of ventricular tachycardia or fibrillation. Congestive heart failure was entered as a characteristic only when it was present in the immediate preoperative period. On the other hand, a history of hypertension alone, irrespective of immediate preoperative blood pressure, was used to include hypertension as a characteristic. Hypokalemia was defined as a serum potassium value of <3.5 mEq/L in the immediate preoperative period (serum potassium values were available in the immediate preinduction period for patients in whom an arterial cannula was inserted, whereas for the remaining patients the latest preoperative serum potassium value available from the medical charts was accepted).

Perioperative myocardial infarction was diagnosed if the patient had an increase in serum levels of CK-MB isoenzyme (>10 IU/L by immunoinhibition/immunoprecipitation technique; 2–10 IU/L is the normal range in the control population at our institute) with the presence of at least one of the two other criteria—chest pain and ECG evidence of subendocardial or transmural myocardial infarction. The diagnosis of PMI was confirmed by an independent cardiologist not directly involved with the patient. Electrocardiographic and CK-MB measurements were performed for 3 consecutive days postoperatively and on the seventh postoperative day in 486 patients with a history of angina, ECG signs of ischemia, postoperative hemodynamic instability, chest pain, dysrhythmias, or signs of ischemia or infarction on the first postoperative electrocardiogram obtained on all 688 patients, and in all the patients who underwent thoracic, abdominal, aortic, or major peripheral vascular procedures. Patients not meeting these criteria were expected to be at a lower risk for adverse cardiac outcome and were discharged from the hospital before 7 days; the intense cardiac monitoring described above was not performed on 202 such patients. Cardiac death was defined as death after PMI, documented cardiac dysrhythmias, or cardiogenic shock, or when death was sudden and unexplained.

Statistical Methods

The data on the 688 patients were subjected to three separate analytic methods: summary statistics, stepwise logistic regression, and discriminant analysis. Twenty-four patient characteristics from preoperative information (Table 1) were selected for the analysis and were tested against the outcomes: good outcome (no PMI, no cardiac death) and adverse outcome (postoperative MI and/or cardiac death). The 24 patient characteristics are not mutually exclusive.

Summary statistics. Summary statistics were performed to calculate 2 × 2 tables, χ^2 values, and P values. For all the 2 × 2 tables Fisher's exact test gave a similar result. Results of the summary statistics are shown in Table 1. The degree of freedom for each characteristic was 1 except for surgical procedures, for which it was 3.

Logistic regression. The patient characteristics from Table 1 were subjected to further multivariate analysis using stepwise logistic regression. A set of seven variables was found so that the P value associated with the introduction of any additional variable was large. These variables were found by a forward selection procedure as well as by fitting the logistic regression model with a large number of variables to see which variables stood out as important. Each

Table 1. Results of Summary Statistics

Preoperative patient characteristics	No. of patients with characteristics	No. of patients with PMI and/or cardiac death (%)	Significance of association
Age >70 yr	349	24 (6.9)	0.227
Male	407	26 (6.4)	0.439
Abdominal, thoracic, aortic, or major vascular surgery	341	28 (8.2)	0.031[a]
Emergency	100	18 (18)	0.000[a]
Previous MI	259	19 (7.3)	0.185
Recent MI (0–3 mo)	24	4 (16.7)	0.111
Chronic stable angina	158	18 (11.4)	0.001[a]
Unstable angina	25	7 (28)	0.000[a]
Previous aortocoronary bypass	130	5 (3.8)	0.287
Congestive heart failure	97	9 (9.3)	0.116
Aortic stenosis	16	1 (6.3)	0.965
Hypertension	349	24 (6.9)	0.227
Diabetes	114	9 (7.9)	0.299
Renal disease	41	3 (7.3)	0.671
Hepatic disease	81	4 (4.9)	0.720
Pulmonary disease	66	6 (11)	0.232
Peripheral vascular disease	177	13 (7.3)	0.313
Bedridden	100	12 (12)	0.004[a]
ECG ischemia	122	18 (14.8)	0.000[a]
ECG atrial dysrhythmia	148	12 (8.1)	0.178
ECG ventricular dysrhythmia	117	9 (7.7)	0.341
ECG conduction abnormality	92	2 (2.2)	0.109
Hematocrit <30	3	0 (0)	0.666
Hypokalemia (serum potassium <3.5 mEq/L)	7	2 (28.6)	0.010[a]

MI, myocardial infarction; PMI, perioperative myocardial infarction.
[a] Significant ($P < 0.05$).

Table 2. Results of Logistic Regression Model

Variable	Estimate	Standard error	χ^2	P	Estimated probability (%)
Emergency	1.28	0.37	11.9	0.0005	0.026 (2.6)
ECG ischemia	1.17	0.37	9.71	0.0018	0.024 (2.4)
Chronic stable angina	1.04	0.37	7.95	0.0048	0.021 (2.1)
Previous MI	0.86	0.42	4.26	0.039	0.018 (1.8)
Age ≥70 yr	0.77	0.39	3.93	0.047	0.016 (1.6)
Aortic or PV surgery	0.72	0.47	2.36	0.12	0.015 (1.5)
Abdominal or thoracic operation	0.68	0.41	2.77	0.09	0.015 (1.5)
Hypokalemia	1.50	0.98	2.36	0.1249	0.034 (3.4)
Intercept[a]	−4.88	0.50	93.69	0.0001	0.008 (0.8)

MI, myocardial infarction; PV, peripheral vascular.
If all the factors are present, $P = 0.959$ (95.9%).
[a] Factor coefficient common to all patients.

series of test steps produced the same set of variables. The results of the model are shown in Table 2.

We further refined the use of a logistic regression model for predicting patient outcomes by randomly dividing our population of 688 patients into two sample groups—observation sample and holdout sample—developing the model from observation sample and using it to predict the outcome in the holdout sample. The random selection, with an assumed probability of selection being 50% for each predictive group, resulted in 318 patients with good outcome (no complications) and 18 patients with adverse outcome (PMI and/or cardiac death) in the observation sample. The outcome was predicted for 352 patients in the holdout sample using the estimates from 336 patients selected to develop the model. This split-sample technique indicated that the model provided highly useful, accurate, and predictive information about patient outcomes as shown in Figure 1, which is a plot of the q values (probability values of adverse outcome derived from observation sample) against the patient number in the holdout sample. Patients with an adverse outcome have their q values plotted as a box, and patients with a good outcome have their q values plotted as a dot. The median of the q values for patients with adverse outcome is 9%, whereas the median of the same for patients with a good outcome is 2%. This difference in the median values (9% vs 2%) shows that the patients with an adverse outcome would indeed have been assigned a much higher probability of that adverse outcome. Conversely, the patients who did not suffer the adverse outcome would have been assigned much lower probability.

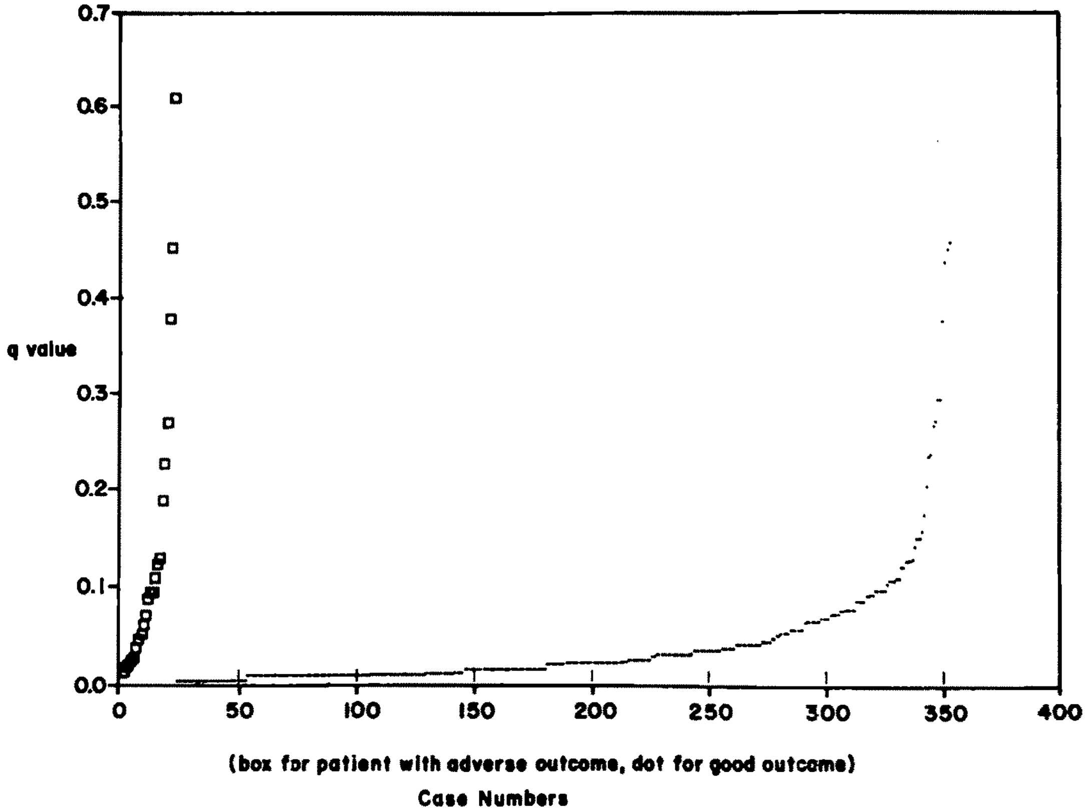

Figure 1. Probability of outcome vs case number in holdout sample. Patients with an adverse outcome have their q values (probability of having an adverse outcome, derived from observation sample using calculations similar to the one shown in Table 3) plotted as a box, and patients with a good outcome have their q values plotted as a dot. The median of the q values for patients with adverse outcome is 9%, whereas the median for patients with a good outcome is 2%. This difference in two median values shows that the probability of adverse outcome is much higher in the patients who had an adverse outcome compared with the group of patients with good outcome.

Discriminant analysis. This method, commonly used in previous studies, assumes that the variables follow a multivariate normal distribution. This is clearly not the situation in this type of problem, but was performed as a comparative test for historic reasons. Not surprisingly, the results were quite similar to the variables described in Table 2. This test was performed by selecting from all variables listed in Table 1 in a stepwise fashion to minimize Wilk's lambda. Closely correlated variables were rejected by setting the tolerance (degree of linear association) to 0.001. Standardized canonical discriminant coefficients were then calculated and used to assess the importance of each factor to the overall discriminant score.

Because we believe that the logistic regression is a more appropriate test for the bivariate outcome, as in our study, we chose not to present data from discriminant analysis. Suffice it to say that about 79% predictive accuracy could be achieved by using the three most important parameters—i.e., chronic stable angina, previous MI, and ECG ischemia.

Results

A total of 688 patients with cardiac diseases and patients who were older than 70 yr of age, all of whom were undergoing noncardiac operations, were included in the investigation. Their ages ranged from 29 to 91 yr (mean age, 67.7 yr). Three hundred forty-nine patients were older than 70 yr of age, 212 of these 349 patients also had significant heart disease; 407 were men and 281 were women; 100 patients underwent emergency operations. One hundred ninety-nine patients underwent thoracic or abdominal operations, and 142 patients underwent aortic or other major peripheral vascular operations; the remaining 347 patients underwent other operations (e.g., neurosurgical, ophthalmic, orthopedic, urogenital, and ear, nose, throat). Five hundred patients had received general anesthesia, 110 patients had received spinal or epidural anesthetics, 11 patients had other regional blocks, and 67 patients received infiltration of local anesthetic at the surgical site supplemented with intravenous sedation. Intraoperative factors—including the choice of monitoring, anesthetic technique, anesthetic drugs, intraoperative hemodynamic changes, and use of ionotropes or vasodilators—did not provide any correlations with the outcome in the initial analysis, and so these intraoperative factors were not included in the stepwise logistic regression analysis.

Incidence of Perioperative Myocardial Infarction and Cardiac Death

Forty patients (5.8%) developed PMI or suffered cardiac death. A total of 32 patients (4.65%) developed PMI. Seven of these 32 patients (21.9%) developing PMI died a cardiac death. Of the eight other patients who did not develop PMI, seven patients succumbed to cardiac death secondary to left ventricular failure or documented ventricular dysrhythmias, and one patient died a sudden unexplained death. Thus, the total incidence of cardiac death was 2.2% (15/688). One hundred fifty-eight patients with chronic stable angina underwent noncardiac operations. The incidence of PMI in these patients with angina was 11.4% (18 patients). Twenty-five patients had unstable angina, and, of these, 28% (seven patients) had an adverse outcome. Of 122 patients with signs of ischemia on preoperative resting electrocardiogram, 12 patients (9.8%) had PMI or suffered cardiac death. Previous MI—either by history or a silent MI diagnosed by ECG criteria—was also an important independent predictor of cardiac risk, as 19 of 259 patients (7.3%) with previous MI experienced adverse outcomes. One hundred patients underwent emergency operations and had an 18% incidence of PMI or cardiac death as compared with 3.7% (22/588) in patients undergoing elective operations. Incidence of adverse outcome was 8.2% (28/341) in patients undergoing abdominal, thoracic, aortic, or major vascular operations, as opposed to 3.5% (12/347) in patients undergoing other operations.

Other Major Postoperative Complications

Of a total of 688 patients, 23 patients (3.3%) developed new congestive heart failure or experienced worsening of preexisting congestive heart failure; 48 patients (7%) developed significant rhythm disturbances or experienced documented ventricular dysrhythmias that did not result in death; 11 patients (1.6%) developed stroke; and 19 patients had episodes of myocardial ischemia documented with ECG changes in the postoperative period that did not result in MI. One patient developed pulmonary embolism confirmed by ventilation/perfusion lung scans. Twenty-five patients (3.6%) developed sepsis. Thus there was an overall incidence of 23% nonfatal but serious complications. These complications were not mutually exclusive. A total of 24 patients (3.5%) died of noncardiac causes such as prolonged sepsis, stroke, and malignancy.

Results of Logistic Regression

Eight characteristics—emergency operation, chronic stable angina, ECG ischemia, previous MI, age (≥70 yr), thoracic and abdominal operations, aortic or peripheral vascular operations, and hypokalemia—had a significant effect on the outcome when considered individually (Table 2).

Prediction of Outcome of Perioperative Myocardial Infarction and/or Cardiac Death

The probability of the adverse outcome of PMI and/or cardiac death can be predicted by using the formula as shown in Table 3. If all the variables are absent, then $P = 0.008$, i.e., the patient has 0.8% chance of developing PMI or suffering cardiac death. The probability of the same outcome calculated with each factor separately is shown in the last column of Table 2. If the patient has all the characteristics then the probability of an adverse outcome is 96%.

Discussion

Many previous investigators have shown that patients with cardiac diseases are at a higher risk for postoperative cardiac complications. These studies have also identified various preoperative risk factors that help in predicting the postoperative outcome (5–7). Other investigators have shown a high prevalence of coronary artery disease in patients undergoing aortic or major peripheral vascular operations (6,8,9). These studies have recommended routine use of preoperative exercise testing, dipyridamole-thallium scanning, and coronary angiography for the assessment of coronary artery disease in this group of patients (8–10). However, none of these studies included a control population or compared their observed complication rates with the rates that would be expected based on a multifactorial assessment of cardiac risk in a general surgical population with preoperative angina (11).

Table 3. Model for Predicting the Adverse Outcome

Z_1 emergency operation
Z_2 angina
Z_3 ECG signs of ischemia
Z_4 previous myocardial infarction
Z_5 age >70 yr
Z_6 abdominal or thoracic operation
Z_7 aortic or peripheral vascular operation
Z_8 hypokalemia

$$P = \frac{\text{Antilogue } x}{1 + \text{Antilogue } x}.$$

where P is the probability of adverse outcome (PMI and/or cardiac death) and

$$x = 1.28\ (Z_1) + 1.04\ (Z_2) + 1.17\ (Z_3) + 0.86\ (Z_4) + 0.77\ (Z_5) + 0.68\ (Z_6) + 0.72\ (Z_7) + 1.5\ (Z_8) - 4.88,$$

where −4.88 is an intercept applicable to all the patients.

If a particular risk factor is present, the corresponding Z factor is replaced by 1. If it is absent, the Z factor is replaced by 0.

EXAMPLE: If the patient has angina and ECG signs of ischemia as risk factors, then

$$x = 1.28(0) + 1.04(1) + 1.17(1) + 0.86(0) + 0.76(0) + 0.68(0) + 0.72(0) + 1.5(0) - 4.88 = -2.67,$$

and antilogue x = 0.069. So $P = 0.069/1.069 = 0.065$. The probability of an adverse outcome in a patient with angina and ECG signs of ischemia would be 6.5%.

ECG, electrocardiographic; PMI, perioperative myocardial infarction.

We studied 688 patients with signs and symptoms of cardiac diseases or who were older than 70 yr of age undergoing noncardiac operations. In a series by Goldman et al. (5) the risk of perioperative cardiac death was increased about 10-fold for patients older than 70 yr of age. This finding by Goldman et al. justifies the inclusion of this group of patients in our study population. Various preoperative risk factors were identified and subjected to multifactorial analysis. Twenty-two percent of patients sustaining PMI died. This finding is consistent with previous studies that have shown a high incidence of mortality in patients sustaining PMI (1–4). These numbers justify selecting PMI and/or cardiac death as end points for adverse postoperative cardiac events. Twenty-four other patients died of noncardiac causes including prolonged sepsis and malignancy. As they did not suffer any primary cardiac event, inclusion of noncardiac death as another outcome end point would have defeated the intent of this study to examine the perioperative cardiac risk.

Eight preoperative risk factors out of the 24 studied were shown to be important as independent and additive predictors of PMI and/or cardiac death. These factors were (a) emergency operation, (b) chronic stable angina, (c) ECG signs of ischemia, (d) previous MI, (e) age >70 yr, (f) abdominal or thoracic operation, (g) aortic or peripheral vascular operation, and (h) hypokalemia. The eighth factor, hypokalemia, had an estimated coefficient large in absolute value but with a high standard error, warning us of considerable uncertainty attached to this estimate. On the other hand, hypokalemia showed up as an independent predictor in spite of a small number of patients with this characteristic, whereas some other factors with a small "n," e.g., recent MI or unstable angina, failed to show up as important independent predictors, thus justifying the inclusion of hypokalemia as a risk factor in the predictive equation. The patient characteristic "bedridden" was important in initial analysis by summary statistics (Table 1) but did not have any importance as an independent predictor. The usefulness of all factors as independent and additive predictors of cardiac risk (PMI and/or cardiac death) was tested by splitting the study population of 688 patients into two groups as described earlier in the statistical section. Various other factors such as recent MI, congestive heart failure, and dysrhythmias have been described as predictors of cardiac risk by some investigators (5,6). They were not found to be significant in our data. The fact that our analysis has shown these factors to be without statistical significance does not imply that these factors are clinically unimportant. The first reason for the lack of significance could be that the patients exhibiting these factors may have been cared for differently as far as their preoperative preparation and perioperative monitoring and management were concerned. The preconceived clinical conception that these patients were sicker and required more vigilance could have played an important role. No attempt was made to control or influence the vigilance or techniques of the attending anesthesiologist. The second reason for lack of significance may be that most previous investigators have included all the patients above the age of 40 yr with or without heart disease, whereas we have included all the patients older than 70 yr and patients younger than 70 yr only if they had a documented heart disease. We also have a large number of patients with chronic stable angina. Thus, these differences in the characteristics of study populations as well as outcome end points could also be responsible for the observed differences in the outcome as well as estimation of predictive factors.

Quite striking were the 11.4% incidence of PMI and/or cardiac death in 158 patients out of a total of 688 patients with chronic stable angina and 28% incidence in 25 patients with unstable angina. Of the remaining 505 patients without angina, only 15 patients (3%) had PMI and/or suffered cardiac death.

Previous investigators, who identified various other preoperative risk factors, have not shown chronic stable angina to be of clinical significance (5–7). Differences in the study population and outcome end points may be partly responsible for the discrepancy between the findings of previous studies and our study. It is also possible that patients with chronic stable angina without any other major risk factors could have been cared for differently with less vigilance. Some of the recent studies on patients with angina in surgical as well as nonsurgical settings have reported results similar to our findings (12–14). Eagle et al. (12), in a recent study of 111 patients undergoing vascular operations, showed that patients with angina and prior MI suffered more postoperative ischemic events than patients without these clinical markers. Roberts et al. (14) showed that 7% per year of patients with chronic angina not treated surgically had suffered a cardiac event. Gill et al. (13) recently showed that history of typical angina, prior MI, and ST-segment depression during thallium exercise testing were important clinical markers for predicting cardiac events. If patients with stable angina, prior MI, and ECG signs of ischemia are at a higher risk for cardiac events in a nonsurgical situation as shown by these recent investigations, they would be expected to be at a much higher risk in the perioperative time period. Thus our findings are consistent with the findings of Roberts et al. (14) and Gill et al. (13) and justify our presumption that differences in the definition of the study population and the outcome end points mentioned earlier are less likely reasons for the discrepancy in the results of previous investigators (5).

Patients with unstable angina and recent MI rarely present for elective noncardiac operations. The risk of cardiac morbidity and mortality is deemed too high. However, 25 patients with unstable angina and 24 patients with recent MI (0–3 mo) underwent urgent or emergent operations in our series. Twenty-eight percent of patients with unstable angina and 16.7% of patients with recent MI had PMI or suffered cardiac death, confirming the conventional wisdom that these patients are at a very high risk for adverse cardiac events. Of 24 patients with recent MI, two patients suffered PMI and two other patients who did not sustain PMI died a cardiac death. Thus, incidence of PMI (only) was 8.4%, but when bivariate outcome of PMI and cardiac death is considered the incidence is 16.7%. This incidence of PMI (only) of 8.4% is not too different from the previous publication by Rao et al. (4). Despite this high incidence of adverse outcome, neither unstable angina nor recent MI showed up as independent predictors on logistic regression analysis. This was due to the small number of patients with this condition in our series. Unstable angina and recent MI must be handled with great caution in surgical patients.

There have been several models suggested for the prediction of cardiac risk in a general surgical population. We attempted to use two models, one suggested by Goldman et al. (5) and the other by Cooperman et al. (6). We found the model suggested by Cooperman et al. to correlate better with our findings. This apparent superiority of latter model could be due to the differences in the statistical models used in these investigations. We used a stepwise logistic regression model, which was also the model used by Cooperman et al., whereas Goldman et al. used discriminant analysis in their investigation. Although prospective reevaluation of our model (Table 3) at some other institute would be ideal, the use of a logistic regression model for predicting patient outcome by splitting our patient population into two groups has successfully shown the usefulness of the approach used in this investigation.

In conclusion, when older patients with cardiac diseases undergo noncardiac operations, patients with angina, previous MI, and ECG signs of ischemia are at increased risk for developing perioperative MI or cardiac death. The probability of an adverse outcome in terms of PMI or cardiac death can be predicted in these patients by using the preoperative risk factors: emergency, age >70, angina, previous MI, ECG ischemia, type of operation, and hypokalemia. Patients with unstable angina and recent MI should be handled with caution in a surgical population, even though these factors did not show up as independent predictors of adverse outcome in this investigation.

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1990;70:248–52

Effect of Volatile Anesthetics on Vecuronium-Induced Neuromuscular Blockade in Children

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PITTET J-F, MELIS A, ROUGE J-C, MOREL DR, GEMPERLE G, TASSONYI E. Effect of volatile anesthetics on vecuronium-induced neuromuscular blockade in children. Anesth Analg 1990;70:248–52.

We studied 60 children undergoing elective surgery to evaluate the effect of interactions between vecuronium and isoflurane or halothane on the potency and duration of neuromuscular blockade, as measured by electromyography. Vecuronium was first administered by a logarithm-based cumulative method (14, 22, 35, 56, 89 μg/kg) in 10 children anesthetized with thiopental (5 mg/kg), alfentanil (15 μg/kg first dose, then 10 μg/kg), and N_2O/O_2 (60:40) until a 95% ± 2% twitch depression (ED_{95}) was obtained. Thirty children given the same balanced anesthesia were then randomly assigned to three groups (n = 10 in each) to receive a single ED_{20} (21 μg/kg), ED_{50} (33 μg/kg), or ED_{80} (47 μg/kg) intravenous bolus of vecuronium calculated from the mean regression line of twitch responses of the first 10 children. In the second part of the study, 20 children were anesthetized with isoflurane (1.2%) or halothane (0.7%) and compared with the previous 10 children anesthetized with alfentanil-N_2O. Potency of vecuronium determined by single-bolus or logarithm-based cumulative techniques was not significantly different. Isoflurane and halothane significantly decreased ED_{50} (22.3 ± 1.6 and 25.4 ± 1.4 μg/kg, respectively; mean ± SE) and ED_{95} (41.5 ± 3.3 and 46.7 ± 3.2 μg/kg, respectively) compared with alfentanil-N_2O (ED_{50}: 32.8 ± 0.8 μg/kg, ED_{95}: 70.5 ± 2.6 μg/kg). Recovery rate from vecuronium-induced neuromuscular blockade was significantly longer with isoflurane than with alfentanil-N_2O or halothane. We conclude that in children single-bolus and logarithm-based cumulative techniques give similar potency estimates for vecuronium. Isoflurane and halothane increase by similar amounts the neuromuscular potency of vecuronium. Finally, the recovery of the vecuronium-induced neuromuscular blockade is significantly prolonged by isoflurane, but not by halothane.

Key Words: ANESTHETICS, ISOFLURANE, HALOTHANE. NEUROMUSCULAR RELAXANTS, VECURONIUM. ANESTHESIA, PEDIATRIC.

Vecuronium is a nondepolarizing intermediate-acting muscle relaxant frequently used in pediatric anesthesia. In adults volatile anesthetics increase the vecuronium-induced neuromuscular (NM) blockade (1), but similar studies have not been reported in children. As MAC values of isoflurane and halothane are significantly greater in children than in adults (2,3), and as dose requirements of vecuronium are also significantly greater in children (4,5), interactions between volatile anesthetics and vecuronium affecting potency and duration of action of vecuronium could differ from those reported in adults (6,7). To study these interactions, administration of vecuronium by the single-bolus technique is required, as previous studies demonstrated that a cumulative dose-response method proposed for studies with long-acting muscle relaxants significantly decreases estimates of the potency of intermediate- or short-acting drugs when compared with data obtained with the single-bolus technique (8,9). Meretoja et al. recently published a logarithm-based cumulative dose-response technique to determine the effect of age on the dose-response relationship of vecuronium during balanced anesthesia (5). They found that ED_{90} of vecuronium in adolescents was comparable to the ED_{90} reported by others in adults, using the single-bolus technique (7,10). However, they did not compare the single-bolus versus the logarithm-based cumulative dose-response technique.

The purpose of the present study was to evaluate the effect of interactions between volatile anesthetics and vecuronium on the potency and duration of

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vecuronium NM blockade in children using a logarithm-based cumulative method to administer vecuronium after validation of this method by comparison with the single-bolus method.

Patients and Methods

Patients

We obtained approval from the institutional ethics committee on human research and informed consent from the parents to study 60 ASA physical status I or II children (age 4.7 ± 0.6 yr [mean ± SD; range 2–9 yr], weight 17.7 ± 1.4 kg) undergoing minor elective surgery.

Comparison Between Single-Bolus and Logarithm-Based Cumulative Dose-Response Techniques

After premedication with diazepam (0.3 mg/kg rectal), anesthesia was induced with 5 mg/kg thiopental and 15 μg/kg alfentanil intravenously and maintained by the administration of N_2O and O_2 (60:40) supplemented with repeated intravenous (IV) doses of alfentanil (10 μg/kg). First, 10 children received incremental IV doses of vecuronium (14, 22, 35, 56, and 89 μg/kg) using the logarithm-based cumulative dose-response technique described by Meretoja et al. (5). The last increment was determined on the basis of individual responses when plotting the dose-response curve during the study period. After each dose, two to three consecutive twitches of equal height were obtained before the next increment was given. In this manner, it was possible to titrate the dose necessary to reach 95% ± 2% suppression of the twitch. Thirty children were then randomly assigned to three groups (n = 10 in each) to receive a single ED_{20} (21 μg/kg), ED_{50} (33 μg/kg), or ED_{80} (47 μg/kg) IV bolus of vecuronium calculated from the mean of individual linear regression slopes of twitch responses (logit effect vs log dose) obtained from data of the first group of 10 children.

Effect of Interactions Between Isoflurane, Halothane, and Vecuronium on the Potency and Duration of Neuromuscular Blockade

A further 20 children were randomly assigned to two equal groups to receive N_2O-isoflurane or N_2O-halothane anesthesia. We used the logarithm-based cumulative technique to compare the potency and duration of vecuronium-induced NM blockade in these children with the values obtained in the previous 10 children anesthetized with repeated IV doses of alfentanil.

After premedication with diazepam (0.3 mg/kg rectal), anesthesia was induced with 5 mg/kg thiopental and 15 μg/kg alfentanil intravenously and maintained with the administration of N_2O and O_2 (60:40) supplemented either with isoflurane (n = 10) or halothane (n = 10) according to the treatment group. The end-tidal concentration of the volatile anesthetics (0.75 MAC excluding N_2O) was age-adjusted: isoflurane, 1.2%; halothane, 0.7% (2,3). These concentrations were maintained during the entire study. The trachea was intubated without muscle relaxant. A multiple gas analyzer (Capnomac, Datex Instrumentarium Corporation, Helsinki) was connected to the endotracheal tube to continuously measure end-tidal CO_2, O_2, N_2O, and halothane or isoflurane concentrations. All children received incremental IV doses of vecuronium using the logarithm-based cumulative dose-response technique, as described above. Ventilation was controlled to keep end-tidal CO_2 between 4.3 and 4.8 vol%. Rectal temperature was maintained between 36.0 and 37.5°C.

Monitoring of Neuromuscular Transmission

Neuromuscular transmission was measured by electromyography (Relaxograph, Datex Instrumentarium Corporation, Helsinki), at the left ulnar nerve-hypothenar muscle, using transcutaneous electrodes. This device delivered supramaximal stimuli (0.1-ms duration) of train-of-four at 2 Hz in every 20 s. The first of the four evoked responses was considered as the twitch height. To minimize movement-induced changes of twitch responses during electromyography measurement, the patient's hand was carefully fixed to avoid any displacement of the electrodes. The Relaxograph was recalibrated just before the administration of vecuronium when a stable anesthetic concentration had been established, i.e., after a 30-min period of unchanged end-tidal concentration of the volatile agent. Twitch responses were measured during this stabilization time in both groups of patients receiving volatile anesthetics as well as for a similar duration in those given balanced anesthesia. To calculate the degree of NM blockade in percentages, all twitch heights were referred to those measured before the first injection of vecuronium. The time to go from the maximal initial blockade to 25%

recovery of twitch height was defined as clinical duration (CD). It does not include the time necessary to obtain maximal NM blockade. The time from 25% to 75% recovery of the twitch height was defined as recovery index (RI). The CD and RI together were defined as D_{75} (duration to 75% recovery). The study was ended when the twitch recovered to 75% of the prerelaxant control level. The administration of the volatile agent was then stopped. Spontaneous or neostigmine-induced (20 μg/kg) recovery of twitch height to control value was obtained. Three patients (one patient in the alfentanil group and two patients in the halothane group) in whom the twitch height did not recover to near 100% were excluded from the study.

Statistical Analysis

To compare both groups of children receiving vecuronium by single-bolus or logarithm-based cumulative technique, the percent twitch depression versus the logarithm of the dose was analyzed by least-squares linear regression. The slopes of the two regression lines were compared by an unpaired Student's *t*-test and the position of the lines compared by analysis of covariance (11).

Using linear regression analysis after logit transformation of twitch responses, we determined the dose-response relationship (logit effect vs log dose) for vecuronium administered by the logarithm-based cumulative technique in each patient of the three anesthetic groups of the second part of the study. All regression slopes were tested with a one-way analysis of variance to determine whether they deviated from parallelism. To compare the potency of vecuronium, ED_{50} and ED_{95} were calculated for each patient from individual linear regression analysis. Comparisons of ED_{50}, ED_{95}, CD, RI, and D_{75} between each group were made using a one-way analysis of variance followed by a Duncan's multiple comparisons test. Finally, a one-way analysis of variance determined whether significant differences existed between anesthetic groups for age, body weight, rectal temperature, or end-tidal P_{CO_2}. For all statistical comparisons, differences were considered significant if $P < 0.05$.

Results

Comparison Between the Single-Bolus and the Logarithm-Based Cumulative Dose-Response Technique

The regression lines of twitch height versus log dose of vecuronium for the single-bolus and the logarithm-based cumulative technique did not significantly deviate from parallelism (Figure 1). Mean ED_{20}, ED_{50}, and ED_{80} of vecuronium were 20.8, 32.8, and 47.1 μg/kg, respectively, determined by the logarithm-based cumulative technique, and 20.1, 34.7, and 48.7 μg/kg, respectively, determined by the single-bolus technique. By analysis of covariance, potency estimates of vecuronium determined by logarithm-based cumulative technique were not statistically different from those obtained by the single-bolus technique.

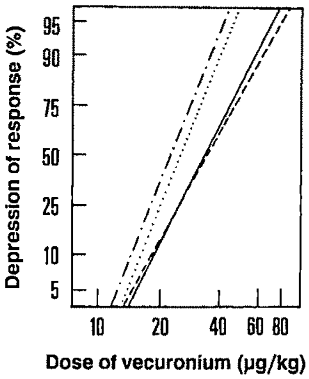

Figure 1. Dose-response curves for vecuronium in children during N_2O/O_2 anesthesia supplemented with alfentanil (——), halothane (· · · ·), or isoflurane (— · —). These three lines are the mean of 10 individual slopes calculated from ED_{50} and ED_{95} values after logit transformation for each anesthetic using the logarithm-based cumulative dose-response technique for administration of vecuronium. For comparison, the *broken line* is the mean regression line of twitch depression vs log-dose of vecuronium in 30 children anesthetized with N_2O/O_2-alfentanil and receiving vecuronium by the single-bolus technique.

Effect of Interactions Between Isoflurane, Halothane, and Vecuronium on the Potency and Duration of Neuromuscular Blockade

The mean slopes of the linear regression analysis of logit of twitch height versus log dose of vecuronium of the three anesthetic groups did not significantly deviate from parallelism (Figure 1). Table 1 describes the potency of vecuronium and the duration of the NM blockade in each anesthetic group.

During alfentanil-N_2O/O_2 anesthesia, ED_{50} and ED_{95} were 32.8 ± 0.8 μg/kg (mean ± SE) and 70.5 ± 2.6 μg/kg, respectively. During isoflurane anesthesia, ED_{50} (22.3 ± 1.6 μg/kg) and ED_{95} (41.5 ± 3.3 μg/kg) were both significantly lower than with alfentanil-N_2O/O_2. Similarly, ED_{50} (25.4 ± 1.4 μg/kg) and ED_{95} (46.7 ± 3.2 μg/kg), measured during halothane anesthesia, were also significantly less than those measured during alfentanil-N_2O/O_2 anesthesia.

The mean time necessary to obtain maximal NM blockade was 7.5 ± 0.3 min in the alfentanil group

Table 1. Potency of Vecuronium and Duration of the Neuromuscular Blockade During N_2O-Alfentanil, Isoflurane, and Halothane Anesthesia in Children

	Alfentanil	Isoflurane	Halothane
ED_{50} (μg/kg)	32.8 ± 0.8	22.3 ± 1.6[a]	25.4 ± 1.4[a]
ED_{95} (μg/kg)	70.5 ± 2.6	41.5 ± 3.3[a]	46.7 ± 3.2[a]
CD (min)	10.6 ± 0.7	10.9 ± 1.1	8.5 ± 0.8
RI (min)	9.1 ± 1.0	13.1 ± 1.9[a]	7.9 ± 0.4
D_{75} (min)	19.7 ± 1.6	24.0 ± 2.7	16.4 ± 1.1

CD, clinical duration (time from initial maximal neuromuscular blockade to 25% twitch recovery); RI, recovery index; D_{75}, time from initial maximal neuromuscular blockade to 75% twitch recovery.

Values are mean ± SE of 10 patients in each group.

[a] Significantly different from N_2O-alfentanil group ($P < 0.05$).

(range 6–9 min), 6.5 ± 0.6 min in the isoflurane group (range 4–9 min), and 7.6 ± 0.4 min in the halothane group (range 6–9 min). The CD was 10.6 ± 0.7 min during alfentanil-N_2O/O_2 anesthesia, and was significantly affected neither by isoflurane nor by halothane anesthesia. The RI was significantly prolonged during isoflurane, but not during halothane, compared with alfentanil-N_2O/O_2 anesthesia (13.1 ± 1.9 min vs 9.1 ± 1.0 min, $P < 0.05$). D_{75} was not significantly different between the three anesthetic groups.

There were no significant differences between the anesthetic groups in body weight, age, rectal temperature, or end-tidal Pco_2. Cardiovascular variables of the three groups of patients were stable during the entire investigation.

Discussion

We have found in the present study that the single-bolus and the logarithm-based cumulative dose-response techniques result in similar potency estimates for vecuronium in children. When compared with alfentanil-N_2O/O_2 anesthesia, isoflurane and halothane significantly enhance the NM blocking effect of vecuronium. Finally, despite a similar 40% reduction of ED_{95} of vecuronium by both volatile anesthetics when compared with alfentanil-N_2O/O_2 anesthesia, recovery of the vecuronium-induced NM blockade is significantly prolonged by isoflurane, but not by halothane.

To determine the potency of vecuronium, the use of the classical cumulative technique described for long-acting muscle relaxants (9) is not appropriate, as larger potency estimates of vecuronium are obtained with this technique than with the single-bolus technique (8). This can be explained by the fact that the effect of the initial dose of vecuronium has worn off before the last dose is given (8). However, the use of the single-bolus technique requires a large number of patients, which makes it difficult to realize such studies, especially in pediatric patients. In order to resolve this problem, we have compared the logarithm-based cumulative technique recently proposed by Meretoja et al. (5) with the single-bolus technique. We did not find any difference in potency estimates of vecuronium between these two techniques. Our data are in accordance with the results of Meretoja and associates (5) who reported a comparable ED_{90} of vecuronium in adolescents, as well as with the results of studies performed in adults, in which the single-bolus technique has been used (7,10). Our results could be explained by the hypothesis that logarithm-based increments of vecuronium may balance for its elimination as, with this technique, the first dose of vecuronium constituted only 20% and the last two doses about 80% of the total dose used. In contrast, in studies using the classical cumulative-dose technique (7,8), the first dose of vecuronium was 40% of the total dose used. Indeed, considering the pharmacokinetics of vecuronium in children (12,13) Meretoja et al. calculated that, in contrast to the classical cumulative technique, the plasma concentration of vecuronium at the time of obtaining the maximal blockade by the logarithm-based cumulative technique would be close to the plasma concentration existing 4 min after injection of the same total dose given in a one-bolus dose (5).

The enhancement of the potency of vecuronium by isoflurane and halothane reported in the present study is similar to that described in adults (6,7), despite differences in MAC values of volatile agents and in dose requirement of vecuronium between children and adults. In children, isoflurane and halothane potentiate in a similar manner the atracurium-induced NM blockade (14), despite differences in end-tidal concentration of volatile agents and methodology of measurement of the NM blockade used in these different studies. As compared with long-acting muscle relaxants, the potency of intermediate-acting NM blocking agents may not be increased by volatile anesthetics in the same degree. Indeed, Miller et al. have reported that isoflurane is two times more effective than halothane in increasing the potency of *d*-tubocurarine and pancuronium (15). It has recently been described that volatile anesthetics and nondepolarizing muscle relaxants may have synergistic prejunctional actions at the neuromuscular junction (16). Although all muscle relaxants produce prejunctional and postjunctional receptor blockade, they may differ in their relative rates of interaction with prejunctional and postjunctional sites (17). These findings may explain the variability of the potentiation of muscle relaxants by different volatile anesthetics. Despite a similar 40% reduction of ED_{95} of vecuronium by both volatile anesthetics, the recovery index was significantly prolonged by isoflurane, but not by halothane, when compared with alfentanil-N_2O/O_2 anesthesia. This effect could be explained by the recently published isoflurane-induced "flickering" of the acetylcholine receptor channel at the NM endplate (18).

In conclusion, the present study demonstrates that in children the single-bolus and the logarithm-based cumulative dose-response technique give similar potency estimates for vecuronium. Isoflurane and halothane increase by a similar amount the neuromuscular potency of vecuronium. Finally, compared with alfentanil-N_2O/O_2 anesthesia, the recovery of the vecuronium-induced NM blockade is significantly prolonged by isoflurane, but not by halothane.

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Azumolene Reverses Episodes of Malignant Hyperthermia in Susceptible Swine

Mark Dershwitz, MD, PhD and Frank A. Sréter, MD, PhD

DERSHWITZ M, SRÉTER FA. Azumolene reverses episodes of malignant hyperthermia in susceptible swine. Anesth Analg 1990;70:253–5.

Azumolene is an analogue of dantrolene with much greater water solubility. Ten swine susceptible to malignant hyperthermia (MH) were triggered into MH episodes via the inhalation of halothane, and azumolene was effective in terminating all of the MH episodes. There was an inverse relationship between the dose of azumolene required to terminate the MH episode and the time it took for the pig to manifest the signs of MH. Azumolene was found to be similar in potency to dantrolene.

Key Words: HYPERTHERMIA, MALIGNANT—azumolene, dantrolene.

Azumolene, 1-[[[5-(4-bromophenyl)-2-oxazolyl]methylene]amino]-2,4-imidazolidinedione, is an analogue of dantrolene with the useful property of much greater water solubility. The standard vial of dantrolene contains 20 mg of the lyophilized drug and 3000 mg of mannitol to facilitate dissolution in 60 mL of water. The solution may still need to be heated to facilitate dissolution of the drug, or be administered through a blood component filter to remove undissolved particles (1). In contrast, azumolene may be prepared in an isotonic solution containing 10 mg/mL, a 30-fold increase in solubility. A comparison of the structures of azumolene and dantrolene is shown in Figure 1.

In experiments studying the physiologic effects of azumolene, the substance has been found to have effects similar to those of dantrolene on muscle tissue obtained from individuals susceptible to malignant hyperthermia (MH). Allen et al. (2) measured the intracellular calcium concentration in vivo in muscle cells from MH-susceptible swine. They found that azumolene caused a dose-dependent decrease in the intracellular calcium concentration in doses ranging from 0.5 to 2.0 mg/kg. These results were similar to those obtained by the same investigators when they studied the effects of dantrolene on cellular calcium levels (3,4). Fletcher et al. (5) studied the effects of azumolene on strips of human muscle obtained from MH-susceptible patients. They found that azumolene antagonized contractures caused by caffeine to the same degree as dantrolene when the drugs were used at the same concentration (10 μM).

The purpose of the present study was to determine whether azumolene could reverse clinical episodes of MH in susceptible swine.

Methods

The study was approved by the Subcommittee on Animal Care of the Massachusetts General Hospital. A herd of Pietrain pigs, inbred for susceptibility to MH, was maintained at the research farm of the Boston Biomedical Research Institute and fed commercial pig diet ad libitum. Offspring of sows and boars known to be susceptible to MH were weaned at age 6–8 wk.

Azumolene was provided by Norwich Eaton Pharmaceuticals, Norwich, N.Y. An isotonic solution of azumolene was prepared using guidelines provided by the manufacturer, and contained 10 mg/mL of azumolene, 2.2% vol/vol glycerol, and potassium hydroxide to adjust the pH to 10.2.

For determination of MH susceptibility, the following procedure was employed. The pig was given 10 mg/kg of ketamine via an intramuscular injection in the rump. After ~10 min, a 22–24-gauge Teflon

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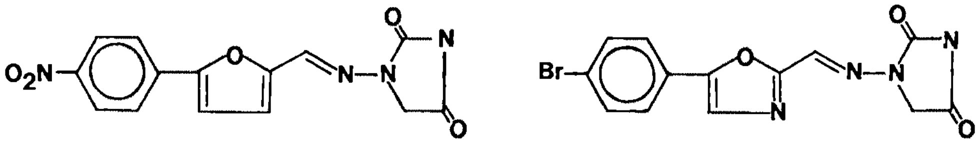

DANTROLENE **AZUMOLENE**

Figure 1. Chemical structures of dantrolene and azumolene.

Table 1. Characteristics of Malignant Hyperthermia-Susceptible Swine Given Azumolene to Reverse the Malignant Hyperthermia Episode

Swine No.	Weight (kg)	Time to hind limb rigidity (min)	Cumulative azumolene dose (mg)
1	11	5	20
2	12	15	10
3	10	20	5
4	13	15	15
5	10	12	10
6	13	26	5
7	16	11	10
8	17	13	15
9	10	30	5
10	13	7	5

Swine 1 and 2, 3–5, 6–8, and 9 and 10 were littermates; all were males.

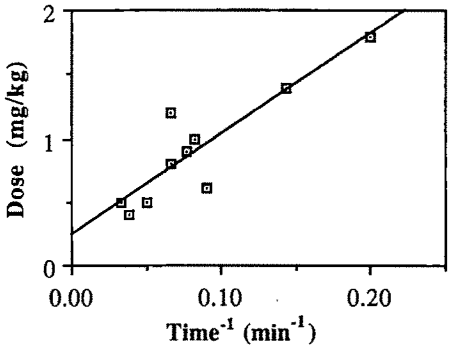

Figure 2. Dose of azumolene required to terminate an MH episode vs 1/time to development of hind limb rigidity. The *line* shows the least-squares fit of the individual data points. For the regression line, $r^2 = 0.799$ and $P = 0.0005$.

intravenous catheter was inserted into an ear vein without complaint from the pig, a normal saline infusion was begun, and electrocardiogram (ECG) leads were applied. The pig was then given 2% halothane and 67% nitrous oxide in oxygen by an anesthesia face mask, allowed to breathe spontaneously, and observed for signs of MH. Minute ventilation was measured with a Wright spirometer, and temperature was determined with a rectal thermistor.

Susceptibility to MH was assessed on the basis of the following clinical criteria: swine responsive to halothane and therefore positive for MH became tachycardic, tachypneic, and manifested rigidity of the hind limbs while breathing halothane. Typically their minute ventilation increased threefold in comparison to that measured during ketamine sedation. Temperature did not change during the short course of these experiments because the halothane was discontinued and the animals were treated with azumolene as soon as muscle rigidity was apparent. Swine nonresponsive to halothane and therefore presumably negative for MH hypoventilated to the point of apnea while breathing 2% halothane and did not manifest hind limb rigidity.

Once the diagnosis of MH had been made, the pig was given 100% oxygen by mask and azumolene intravenously in 5-mg increments, waiting 2 min between doses, until the hind limbs were supple. The pigs were allowed to recover and returned to the farm.

Results

Azumolene was administered to ten MH-susceptible swine after they had been triggered into an MH episode by the inhalation of halothane. In each case, the episode was terminated by a dose of azumolene of <2 mg/kg. Table 1 shows the characteristics of the individual swine and the cumulative doses of azumolene required to terminate the MH episode. There was an inverse relationship between the time required for development of hind limb rigidity and the total dose of azumolene required to reverse such rigidity. Thus, swine that were more sensitive to the triggering effect of halothane (and that more rapidly developed signs of MH) required a larger dose of azumolene to reverse the MH episode. This relationship is shown in Figure 2.

Discussion

The major disadvantage to the use of dantrolene during an episode of MH is its lack of water solubility and difficulty in preparing a solution suitable for intravenous administration. Indeed, Gronert (1) has stated that the process of preparing dantrolene solutions during an MH crisis "will require the full time efforts of three or four people." In addition, the solutions may need to be heated to facilitate dissolution, or administered through a blood component filter to remove undissolved drug (1).

Azumolene may represent a significant improvement in the therapy of MH. Its solubility of 10 mg/mL in an isotonic solution, in comparison to that of dantrolene in a hypertonic mannitol solution (0.33 mg/mL), means that a therapeutic dose may be administered employing 1/30th the volume. Thus, a 70-kg patient who required 2 mg/kg of drug to reverse an MH episode could have the total dose of azumolene contained in two 10-mL syringes, in contrast to dantrolene contained in seven 60-mL syringes, saving much critical time.

The data in Table 1 show that the ED50 for azumolene is ~0.85 mg/kg. In our experience with our herd of MH-susceptible swine, we have used an initial dantrolene dose of 1 mg/kg, and repeated this dose if necessary to terminate an MH episode (6). Using dantrolene to terminate nearly 100 episodes of MH, we have found that a dose of 1 mg/kg was effective in ~80% of the pigs, whereas the remainder had their episodes reversed by a dose of 2 mg/kg (data not shown). Therefore, azumolene appears to be approximately equipotent with dantrolene in terms of reversal of MH episodes, in agreement with previous studies comparing the physiologic effects of the two drugs (2–5).

Further studies are needed on the toxicity of the drug in laboratory animals and on the stability of the drug in solution. Based on the results of such studies, azumolene may be a candidate for studies in human MH.

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1990;70:256–61

Comparison of Patient-Controlled Epidural Analgesia and Conventional Intermittent "Top-Up" Injections During Labor

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GAMBLING DR, McMORLAND GH, YU P, LASZLO C. Comparison of patient-controlled epidural analgesia and conventional intermittent "top-up" injections during labor. Anesth Analg 1990;70:256–61.

In a prospective, randomized manner, bolus injection patient-controlled epidural analgesia (PCEA; n = 30) and conventional intermittent "top-up" injections (CIT; n = 28) of bupivacaine in nulliparous parturients during first stage of labor were compared. Group A (PCEA) patients self-administered, using a patient-controlled analgesia device, 4-mL increments of 0.125% bupivacaine with 1:400,000 epinephrine, to a maximum 12 mL/h as required. Group B (CIT) patients received 12 mL of the same solution, on request, from the anesthesiologist. Hourly assessments of pain relief (visual analogue scale), satisfaction, sensory and motor block, blood pressure, and cervical dilatation were made. In addition, retrospective pain assessments were made in patients requesting analgesia in the preceding hour, indicating their maximum pain during that time.

The groups were demographically comparable and equally low hourly bupivacaine requirements were seen (group A, 6.36 ± 0.43 mg; group B, 6.23 ± 0.39 mg) producing similar mean sensory levels. Pain relief obtained in both groups was similar but was associated with greater satisfaction in patients using PCEA (P < 0.05).

This study shows that PCEA is a viable alternative for providing pain relief in the first stage of labor.

Key Words: ANESTHESIA, OBSTETRICS—epidural. ANESTHETICS, LOCAL—bupivacaine. PAIN, LABOR. EQUIPMENT, PATIENT-CONTROLLED ANALGESIA.

The use of patient-controlled analgesia (PCA) by the intravenous route in obstetrics, both during labor (1,2) and after cesarean section (3,4), has been well documented. The application of other routes for PCA, including injections into the epidural space, has also been described. Patient-controlled epidural analgesia (PCEA) was initially shown to be effective using meperidine and morphine in postoperative patients (5). It has also been effective in oncological patients.

Our group had demonstrated the efficacy of PCEA during labor using injections of dilute local anesthetic solutions into the epidural space (6). We used a PCA method that utilized a bolus injection plus a continuous, fixed-rate infusion. Other authors have also described the efficacy of this technique (7), as well as the superiority of the combination of local anesthetic and fentanyl compared with local anesthetic alone.

This present study was designed to compare, in a prospective, randomized and controlled manner, bolus-only PCEA with conventional intermittent "top-up" injections (CIT) of local anesthetic, provided by the anesthesiologist, for women in the first stage of labor.

Methods

Sixty ASA physical status I or II nulliparous parturients in established term labor were selected over a 12-mo period. Each patient had requested epidural analgesia for pain relief and had a singleton fetus in vertex presentation. Before the study, approval had been obtained from both hospital and university Screening Committees for Research Involving Human Subjects. Informed consent was obtained from each patient, once they were comfortable and able to concentrate on the study details being presented to them.

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Using a standard technique, an epidural catheter was inserted through either a L3-4 or L2-3 interspace with correct position of the catheter assessed using a 3-mL test dose of 0.25% bupivacaine. After 3 min a further 5 mL of the same solution was given to produce at least a T-10 sensory block. Once a satisfactory sensory level was obtained the patients were randomly assigned to one of two groups. The randomization was computer generated in blocks of six, so that the two groups would be balanced.

Group A (PCEA) patients were instructed to self-administer 4-mL increments of 0.125% bupivacaine with 1:400,000 epinephrine once they became aware of a return of pain. No limit was imposed on the patient in terms of the number of demands she could make and it was made clear that she could not overdose herself as we had preselected safe dosing parameters. The PCA device used was an Abbott Lifecare Infuser and a lockout period of 20 min was selected. Thus the maximum hourly dose of bupivacaine available to the patient was 15 mg.

Group B patients received 12 mL of 0.125% bupivacaine with 1:400,000 epinephrine via the epidural catheter on request from the anesthesiologist. The maximum hourly dose of bupivacaine available to these patients was also 15 mg.

Supplemental analgesia was provided to patients in both groups in the event of inadequate analgesia from either persistent occipito-posterior position or missed thoracic segments. Increments of 3–5 mL of 0.25% or 0.5% bupivacaine were the only supplements used.

The study began with administration of a test dose and was concluded when the second stage was reached, or a decision had been made to perform a cesarean section. The following scheduled assessments were made 30 and 60 min into the study and then hourly:

(a) Pain score; the patient using a 10-cm vertical visual analogue scale
(b) Satisfaction scores; the patient again using a 10-cm vertical visual analogue scale
(c) Sensory level, determined by loss of sensation to cold, using an ice cube
(d) Degree of motor block, using Bromage's scale
(e) Maternal blood pressure
(f) Fetal heart rate (continuously monitored)
(g) Cervical dilatation

An additional, retrospective assessment of pain relief was also made at each scheduled assessment, but only if a dose of local anesthetic had been administered in the preceding hour. In that event patients were asked to indicate, using the 10-cm scale, their maximum pain score during the preceding hour. These were designated as interhourly pain scores, but were only measured in the final 38 patients studied.

Pain scores were analyzed in two different ways. First, all the scheduled pain scores were converted to produce a pain relief index. This provided us with the percentage of pain relief obtained at any assessment time relative to the pain score made before epidural analgesia. Pain relief index = 100 − (actual pain score divided by baseline pain score × 100).

In addition, both scheduled and interhourly pain scores were placed into one of three clinically descriptive categories, each representing a portion of the pain scale. Scores from 0 to 3 were placed into category 1, representing no pain or mild discomfort only. Scores of >3 but ≤ 5 designated as moderate pain, became category 2, and scores >5 were placed into category 3, representing severe pain.

Additional data collected included (a) duration of first and second stages of labor; (b) complications of labor and delivery; (c) neonatal Apgar scores at 1 and 5 min; and (d) total dose of bupivacaine used during the study period.

The initial 8 mL of 0.25% bupivacaine was not included in the calculation of local anesthetic requirements, but any supplemental bupivacaine was included. This was done to avoid any bias in the results due to inclusion of patients with very short labors.

Demographic data were analyzed using Student's t-test, χ^2 analysis, and, where applicable, Fisher's exact test. Differences in scheduled pain scores, interhourly pain scores, and satisfaction scores were first analyzed with repeated measurements analysis of variance and a difference was declared significant if $P < 0.05$. The scheduled and interhourly pain assessments were also categorized into three levels of pain (none/mild, moderate, severe) and a Fisher's exact test was done at each time point (i.e., 30 min, 1 h, . . .) to test whether the distribution of patients among those three categories was different for the PCEA and CIT groups. Here we declared a difference significant only if $P < 0.005$, as we were performing multiple tests. A Spearman correlation was performed to analyze the relationship between pain relief and patient satisfaction at each assessment period. All results are reported as mean values ± standard error.

Results

A total of 58 women were studied, 30 in group A and 28 in group B. Two patients were taken out of the study from group B, one because she developed

Table 1. Patient Demographics

	Group A (PCEA) (*n* = 30)	Group B (CIT) (*n* = 28)
Maternal age (yr)	32.7 ± 0.74	31.0 ± 1.1
Height (cm)	164.8 ± 1.4	160.7 ± 1.7
Weight (kg)	75.2 ± 1.9	71.4 ± 2.1
Cervical dilatation at start of study (cm)	3.6 ± 0.25	4.1 ± 0.26

CIT, conventional intermittent "top-up" injections; PCEA, patient-controlled epidural analgesia.
Values are mean ± SE.

Table 2. Results: Labor and Vaginal Delivery

	Group A (PCEA) (*n* = 30)	Group B (CIT) (*n* = 28)
Duration of study (h)	6.09 ± 0.57	5.70 ± 0.55
Duration of labor (h)		
First stage	15.3 ± 1.4	13.7 ± 0.8
Second stage	2.3 ± 0.26 (*n*=21)	1.9 ± 0.22 (*n*=23)
Hourly bupivacaine dose (mg)	6.36 ± 0.43	6.23 ± 0.39

CIT, conventional intermittent "top-up" injections; PCEA, patient-controlled epidural analgesia.
Values are mean ± SE.

Table 3. Results: Mode of Delivery

	Group A (PCEA)	Group B (CIT)
Spontaneous	7	9
Vacuum	1	1
Forceps	13	13
Cesarean section	9	5
Total	30	28

CIT, conventional intermittent "top-up" injections; PCEA, patient-controlled epidural analgesia.

preeclampsia and the other because of a displaced epidural catheter that had to be replaced.

There were no significant differences between the groups in terms of maternal age, height, weight, or cervical dilatation at the start of the study (Table 1).

Both groups were similar with respect to duration in the study, duration of both stages of labor, and the hourly dose of bupivacaine used (group A, 6.36 ± 0.43 mg vs group B, 6.23 ± 0.39 mg; see Table 2). Table 3 shows the various types of delivery. A higher cesarean section rate was seen in group A, but this was not significantly different from that of group B.

Neonatal birthweight was similar in both groups but there was a higher number of neonates with Apgar scores of <7 at 1 min in the study group. At 5 min there were no differences in Apgar scores (Table 4).

Table 4. Results: Neonatal Data

	Group A (PCEA)	Group B (CIT)
Neonatal birthweight (kg; mean ± SE)	3.46 ± 0.08	3.54 ± 0.08
No. of neonates with Apgar scores <7		
At 1 min	6	3
At 5 min	0	0

CIT, conventional intermittent "top-up" injections; PCEA, patient-controlled epidural analgesia.

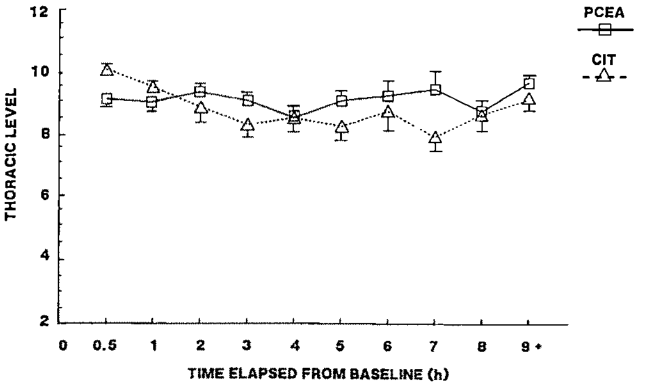

Figure 1. Thoracic sensory levels (mean ± SEM) versus time (h).

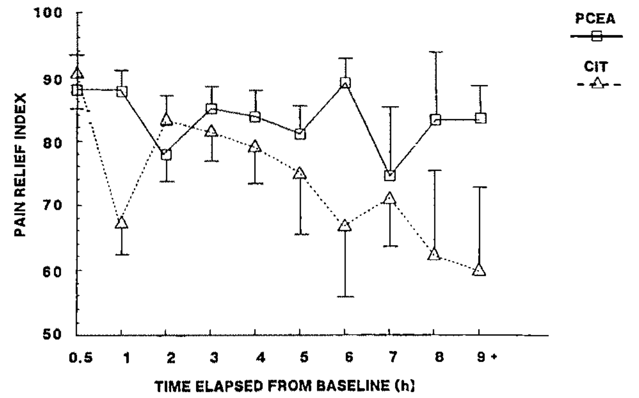

Figure 2. Pain relief obtained throughout the study expressed as pain relief index (PRI). P = NS; PRI = 100 − (actual pain score divided by baseline pain score × 100).

There was no significant difference in the number of patients requiring supplemental analgesia (six in group A vs eight in group B), and mean thoracic sensory levels did not differ significantly at any observation point (see Figure 1).

Figure 2 shows the degree of pain relief obtained by patients in both groups at each scheduled observation point. It is expressed here as the pain relief index in that the amount of pain relief described is based as a fraction that takes into account the initial preepidural pain score. For example, if the initial preepidural pain score was 10 and the pain score at a subsequent observation point was 2, this would indicate a pain relief index of 80%. If the initial pain score (preepidural) was 8 and the pain score at a

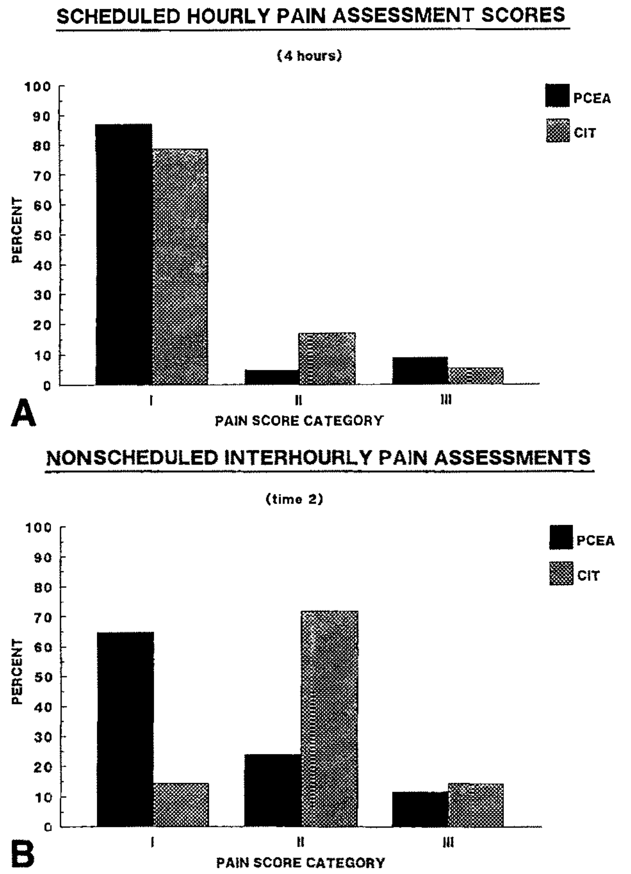

Figure 3. Pain score categories with PCEA and CIT (see Figure 1) 4 h after baseline pain score measurements (**A**). Changes in pain score categories with PCEA and CIT between 30 min after and 90 min after baseline pain score measurements. These represent the maximum pain felt before a request for additional analgesia (**B**). Category 1—no pain to mild pain (pain score 0–3); category 2—moderate pain (pain score >3 but <5); and category 3—severe pain (pain score >5).

subsequent observation point was 2, this would represent a pain relief index of 75%. Although there is a trend toward a higher pain relief index in the PCEA group, this was not significantly different from the CIT group ($P = 0.15$). The observed differences were not the result of lower preepidural pain scores in the CIT group, as the mean value for that parameter was the same in both groups (group A, 8.43 ± 0.21 vs group B, 8.56 ± 0.19).

Figure 3A shows the distribution, 4 h postbaseline, of the total number of scheduled pain scores when divided into the three clinical categories described earlier. Each column represents the percentage of the total pain score assessments made in that particular category. The total number of scheduled assessments at this time point was 22 in group A and 18 in group B. The differences observed in the distribution of the pain scores did not achieve statistical significance.

Figure 3B shows the distribution of interhourly pain scores into the same three pain categories at time 2 (pain scores taken 30–90 min from the baseline were classified as time 2). Again the vertical axis represents the number of interhourly pain score assessments as a percentage of the total and the horizontal axis is divided into the three pain categories. There were 17 interhourly assessments in group A and seven in group B at time 2. Although there was a trend toward superior pain relief in favor of PCEA, as shown by these examples, overall these did not achieve statistical significance by any of our analyses.

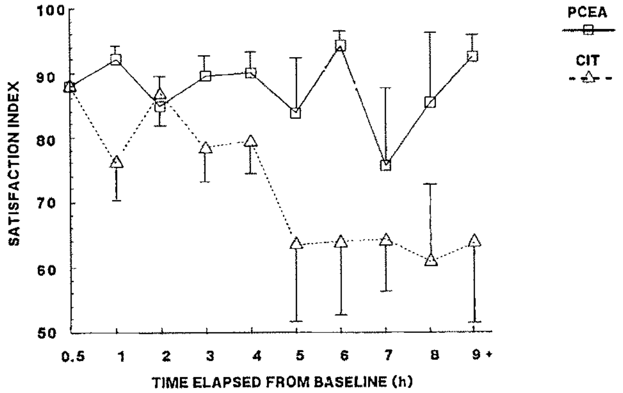

Figure 4. Patient satisfaction throughout the study expressed as satisfaction index (SI). $P < 0.05$; SI = 100 − (actual satisfaction score divided by baseline satisfaction score × 100).

There was a statistically significant difference in patient satisfaction ($P < 0.05$) between groups in favor of PCEA (see Figure 4).

There was no significant motor block in patients from either group and no cases of hemodynamic instability were observed. There were no mishaps due to malfunctioning of the PCA device.

Discussion

This study has shown that bolus-only PCEA, using a dilute bupivacaine solution with epinephrine, provides equal pain relief during the first stage of labor when compared with CIT provided by an anesthesiologist upon request, but is associated with greater patient satisfaction. Very low local anesthetic requirements were observed in both groups. Patients in group A could titrate small boluses of local anesthetic which provided a consistent thoracic sensory block, avoiding—in most cases—the return of a significant degree of discomfort. As both resident and staff anesthesiologists are always available in our institution, long delays in providing a top-up injection for group B patients did not occur, which may explain similarities in the quality of pain relief obtained.

When compared with the results of our previous study (6), which looked at PCEA bolus plus a constant background infusion of 0.125% bupivacaine in a similar patient population, the hourly local anesthetic requirement is almost halved when bolus-only PCEA is employed. This may be a result of adding 1:400,000 epinephrine to the local anesthetic solution, which can prolong the duration of the block and improve its quality. A further study comparing the two methods, and using the same drug, will be required to assess whether or not the background infusion is redundant.

Epidural analgesia during labor is often managed by CIT of local anesthetic. These are administered by an anesthesiologist, nurse anesthetist, obstetric nurse, or midwife, on demand from the parturient. Return of pain is the trigger for the top-up request and if a delay in administering local anesthetic occurs, pain can very rapidly return to intolerable levels. In addition, as labor progresses analgesic requirements may increase, so that the pain experienced after a delay in receiving the top-up may be worse than that experienced before epidural insertion.

This common occurrence prompted an editorial in the Lancet (8), which coined the term epidural "catch-up." A continuous epidural infusion of local anesthetic can overcome the problem of a return of pain in most cases, but at the expense of higher dose requirements (9) and the potential for the development of motor paralysis and tachyphylaxis.

Patient-controlled analgesia is a means of attaining optimal analgesia (10), and there are many studies that show excellent analgesia, high patient satisfaction, and low dose requirements in postoperative patients using intravenous PCA narcotics (11). Applying the PCA concept to epidural analgesia in labor is logical and may overcome the potential problem of the "catch-up" phenomenon associated with CIT by providing the patient with control over local anesthetic administration.

Regular scheduled top-up injections provided by a midwife have produced excellent analgesia (12), but this practice could be associated with the administration of more drug than the patient actually needs. Ideally, a midwife or anesthesiologist would administer the local anesthetic as soon as discomfort starts to return, thus avoiding an unpleasant return of pain. Unfortunately, in many busy practices this ideal cannot be achieved so PCEA may be a useful alternative in this setting.

Pain relief can also be improved when control is handed to the patient because of the psychological factors involved (13), the placebo effect, and because only the patient knows exactly how bad the pain is and how much she can tolerate (14). By reducing the time between patient demand for pain relief and onset of action of the drug given to relieve pain, which is optimal with PCA, patient anxiety is further reduced, thus minimizing another factor that can exacerbate pain. These factors may have contributed to the superior satisfaction scores seen in patients using PCEA in this study. We accept that investigator bias cannot be ruled out though, as this was not a blinded study. Even so, the patient was fully instructed on the use of the pain scales before randomization and filled the score in herself with no further direction from the investigator.

Patient-controlled epidural analgesia provides us with a valuable research tool for comparing the efficacy of various concentrations of different local anesthetics, either alone or in combination with narcotics. As has been studied with intravenous PCA (15,16). varying the bolus dose and lockout periods with PCEA may also produce useful information.

Finally, it would be of interest to consider the effects of self-administered intrathecal injections, given inadvertently, in the case of a misplaced epidural catheter. Van Zundert and colleagues (17) have described the effect of injecting 10 mL of 0.125% bupivacaine with 1:800,000 epinephrine via a 25-gauge spinal needle over a 30–60-s period in pregnant women. He found a maximum sensory block of T-2 (range C-5 to T-5) after 15 min, with no evidence of respiratory depression or hand grip weakness. Significant motor blockade occurred within 5 min and was complete at 25 min. Hypotension was not a serious problem, occurring in 12% of patients, and easily treated. As the local anesthetic solution he used was similar to that used in our study, one can only assume that similar changes would be seen in our patients after two or three self-administered intrathecal injections, although it is possible that in a laboring patient anesthetic spread may be more extensive. Conversely, the doses are well spaced apart so in fact the clinical signs might be more subtle with a PCEA technique. No patients in the present study, or indeed any who have received PCEA in our hospital, have had this problem. When all epidural analgesic injection techniques are considered, the occurrence of misplaced epidural catheters into the subarachnoid space in our institution is extremely rare, but we still have a protocol in place that would allow a nurse-midwife to recognize early signs of this condition.

In summary, bolus-only PCEA effectively provided satisfactory pain relief during labor with very low local anesthetic requirements. Patient-controlled epidural analgesia provided equal pain relief but with superior patient satisfaction throughout the study when compared with CIT. In the majority of patients, overall satisfaction is directly related to the degree of pain relief obtained.

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Pharmacokinetics of Ropivacaine in Nonpregnant and Pregnant Ewes

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SANTOS AC, PEDERSEN H, SALLUSTO JA, JOHNSON HV, MORISHIMA HO, FINSTER M, ARTHUR GR, COVINO BG. Pharmacokinetics of ropivacaine in nonpregnant and pregnant ewes. Anesth Analg 1990;70:262–6.

The pharmacokinetics of ropivacaine were studied in chronically instrumented nonpregnant and pregnant ewes. On the day of study, the urinary bladder was catheterized. Ropivacaine (2.5 or 3.0 mg/kg) was administered by intravenous infusion over 2 or 4 min. Serial samples of arterial blood and urine were collected over 5 h, and drug concentrations were determined using a gas chromatographic technique. Total clearance of ropivacaine was lower in the pregnant animals (21.6 ± 4.5 $mL \cdot min^{-1} \cdot kg^{-1}$) compared with the nonpregnant animals (45.1 ± 6.7 $mL \cdot min^{-1} \cdot kg^{-1}$). There was a tendency toward a decrease in the volume of distribution during the terminal exponential phase of drug elimination of 2.03 ± 0.36 L/kg in the pregnant and 4.32 ± 1.03 L/kg in the nonpregnant sheep. Thus the difference in the elimination half-life was only minimal: 74.7 ± 10.7 min in the pregnant and 64.4 ± 7.4 min in the nonpregnant animals. It is concluded that ovine pregnancy is accompanied by changes in the pharmacokinetics of ropivacaine. Inadvertent intravenous injections of similar drug doses to pregnant and nonpregnant women might result in higher plasma concentrations of ropivacaine in the former. However, the rate of decline in plasma levels of the drug would be similar in both.

Key Words: ANESTHETICS, LOCAL—ropivacaine. PHARMACOKINETICS, ROPIVACAINE. PREGNANCY, PHARMACOKINETICS—ropivacaine. ANESTHESIA, OBSTETRICAL.

Ropivacaine is a new amide local anesthetic that is structurally related to bupivacaine. Its potency and duration of action are similar to that of bupivacaine, but its cardiotoxicity may be less (1,2). If this is proven to be so, these properties would make ropivacaine a desirable drug for regional anesthesia in obstetrics.

Disposition of local anesthetics during pregnancy may be affected by gestational changes in body-fluid volume and composition, as well as by hemodynamic alterations. However, there are relatively few studies pertaining to the effects of pregnancy on local anesthetic pharmacokinetics. In the case of lidocaine, the volume of the central compartment, the total distribution volume, and clearance have been shown to be greater in pregnant than in nonpregnant ewes when the drug is given by intravenous infusion (3,4). The purpose of this study is to investigate the pharmacokinetics of ropivacaine in pregnant and nonpregnant ewes, and to determine its fetal effects.

Materials and Methods

Nine nonpregnant and eight pregnant ewes near term of gestation (term = 148 days) were studied according to a protocol approved by the Institutional Animal Care and Use Committee. The details of surgical preparation have been previously described (5). Briefly, after an overnight fast, ewes were given spinal anesthesia with 10–12 mg of tetracaine hydro-

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chloride. A femoral cut-down was performed and the femoral artery and vein were cannulated with polyethylene catheters. Pregnant ewes also underwent laparotomy and hysterotomy for cannulation of the fetal common carotid artery and jugular vein. Before uterine closure, a catheter was placed in the amniotic cavity. All catheters were tunneled subcutaneously and exteriorized within a pouch attached to the ewe's flank. Two nonpregnant and four pregnant ewes had catheters inserted into the jugular vein and carotid artery (under local infiltration) instead of into the femoral vessels. Pregnant animals recovered for 4–5 days before study, the nonpregnant ones for at least 3 days.

On the day of the experiment, the ewe was contained in a cart with freedom to stand or lie down. Food and water were freely available. A Foley catheter was placed on the morning of study in the majority of animals for urine collection.

After a control period of 30–60 min, 0.5% ropivacaine HCl was infused intravenously. Three nonpregnant and one pregnant ewe received 2.5 mg/kg of the drug over 2 min. To reduce toxic manifestations, the infusion was extended to 4 min in the remaining animals, but the dose was increased to 3.0 mg/kg so as to assure measurable plasma concentrations of the drug for a period long enough to obtain accurate measures of pharmacokinetic indices.

Throughout the study, the heart rate and blood pressure of the ewe (and where appropriate, the fetus) were monitored and recorded on a polygraph. Arterial blood samples from the adult (and fetus) were obtained in heparinized syringes before and at the end of drug injection, and at 1, 2, 5, 10, 15, 30, 60, 90, 120, 180, 240, and 300 min thereafter. Aliquots of arterial blood samples, obtained before and at the end of drug injection, as well as at 5 and 60 min thereafter, were analyzed for pH and blood gases using appropriate microelectrodes. Samples were then centrifuged, and the plasma was separated and frozen. Starting at 15 min, urine samples were collected, volume determined, and an aliquot frozen. Plasma and urine samples were subsequently analyzed for ropivacaine concentrations using a gas chromatographic technique similar to that described by Tucker (6). The assay was calibrated to measure concentrations down to 5 ng/mL. The day-to-day coefficient of variation throughout the study ranged from 9% at 0.05 μg/mL to 2% at 1 μg/mL.

A two-compartment open model was used to describe the resulting concentration data. Initial estimates of the elimination rate constant (β) were determined by linear regression analysis and, using the method of residuals (7), values for the distribution rate constant (α) were derived. Initial estimates of the volume of central compartment (Vc) and microconstants (K_{12}, K_{21}, K_{10}) were determined by standard equations (8), using a correction factor for infusion (9). Pharmacokinetic data were generated from these estimates with a computer program employing an opportunistic, nonlinear regression method (SIMPLEX) based on the algorithm of Nelder and Mead (10). Plasma concentrations of drug were weighted according to the method of Ottaway (11), which resulted in greater weighting to the lower concentrations during the elimination phase.

Differences in derived pharmacokinetic indices and urinary excretion of ropivacaine between nonpregnant and pregnant ewes were compared using Student's *t*-test for unpaired data. Changes from control in heart rate, blood pressure, pH, and gas tensions were evaluated by analysis of variance for repeated measures. A $P < 0.05$ was considered statistically significant. Power of statistical analysis was determined where required. All results are expressed as the mean ± SEM.

Results

The mean gestational age in pregnant animals was 133 ± 1 days. They weighed 64.5 ± 1.7 kg; the weight of nonpregnant ewes was 56.6 ± 3.0 kg. Three nonpregnant and one pregnant ewe were given 2.44 ± 0.08 mg/kg of ropivacaine over 2 min. As they developed early signs of local anesthetic toxicity, manifested by tremors, the remaining animals were given the drug infusion over 4 min—2.85 ± 0.13 mg/kg to nonpregnant ($n = 6$) and 2.86 ± 0.09 mg/kg to pregnant sheep ($n = 7$).

The highest mean plasma concentrations of ropivacaine were measured in samples obtained at the end of drug infusion. In three nonpregnant sheep given the brief infusion it was 4.48 ± 0.94 μg/mL, and in those given the drug over 4 min, 4.18 ± 0.45 μg/mL. In the only pregnant ewe given the drug as a short infusion, the resulting peak plasma concentration was 7.84 μg/mL. In the remaining pregnant ewes given the drug over 4 min, it was 5.45 ± 0.57 μg/mL (Figure 1). The subsequent decline in plasma concentrations could be described by a biexponential equation in both the nonpregnant and pregnant sheep. The highest fetal plasma concentrations of ropivacaine were measured in the first 2 min after the end of maternal drug administration. At 1 min, the plasma concentration was 0.74 ± 0.04 μg/mL in the fetuses of ewes given the drug over 4 min ($n = 4$, due to technical difficulties in sampling the remaining

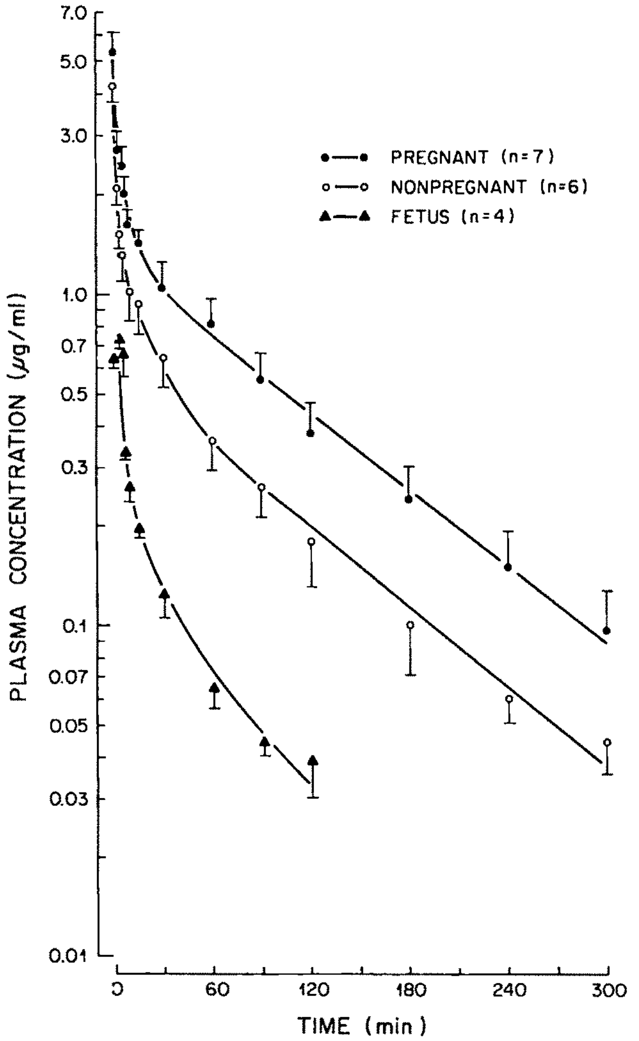

Figure 1. Ropivacaine plasma concentrations (µg/mL) in the pregnant, nonpregnant, and fetal sheep after a 4-min intravenous infusion of the drug to the adult animal (mean ± SEM).

three fetuses), and was 0.60 µg/mL in the fetus whose mother received the brief infusion.

Hemodynamic, acid-base, and pharmacokinetic data from both 2- and 4-min infusion groups were similar, and were therefore combined for the purpose of analysis. All adult ewes and fetuses were in good condition before the study. Ropivacaine injection did not result in significant changes from control in adult or fetal heart rate, mean arterial blood pressure, pH, and blood gas tensions measured at the end of infusion, and at 5 and 60 min thereafter (Table 1).

Derived pharmacokinetic indices are listed in Table 2. The distribution half-life ($t_{1/2\alpha}$) was similar in both groups of ewes, being 3.3 ± 0.7 min in the nonpregnant and 2.7 ± 1.1 min in the pregnant animals. The elimination half-life ($t_{1/2\beta}$) was also similar: namely, 64.4 ± 7.4 and 74.7 ± 10.7 min in nonpregnant and pregnant sheep, respectively.

Total body clearance (Cl) of ropivacaine was significantly less in pregnant ewes, 21.6 ± 4.5 $\text{mL}\cdot\text{min}^{-1}\cdot\text{kg}^{-1}$ compared with 45.1 ± 6.7 $\text{mL}\cdot\text{min}^{-1}\cdot\text{kg}^{-1}$ in nonpregnant animals. There was a strong tendency for the volume of distribution during the terminal exponential phase of drug elimination (Vd_β) and the volume of distribution at steady state (Vd_{ss}) to be lower in pregnant animals. These were 4.32 ± 1.03 and 2.96 ± 0.55 L/kg, respectively, in nonpregnant ewes, compared with 2.03 ± 0.36 and 1.69 ± 0.27 L/kg, respectively, in pregnant ewes ($P = 0.053$ and 0.056). The power of statistical analysis was 50% for Vd_β and 40% for Vd_{ss}.

Data regarding urinary excretion of unchanged ropivacaine in six nonpregnant (catheter could not be inserted in two animals, and, in one, urine collection was incomplete) and seven pregnant ewes are listed in Table 3. The total amount of unchanged ropivacaine and the proportion of the dose recovered in the urine over the 300-min sampling period were lower in pregnant animals compared with nonpregnant ones. These were 0.19 ± 0.05 mg and 0.01% ± 0.02%, respectively, in the pregnant and 0.53 ± 0.13 mg and 0.36% ± 0.1%, respectively, in the nonpregnant group ($P < 0.05$). The total amount of ropivacaine recovered did not exceed 1 mg in any individual animal.

Discussion

Our data indicate that the Cl of ropivacaine was significantly lower in pregnant than in nonpregnant ewes. Also, there was a tendency toward a decrease in Vd_β with minimal change in $t_{1/2\beta}$. The change in Vd_β (as well as in Vd_{ss}) might have reached statistical significance with a greater power of analysis. The reduction in Cl may be due in part to pregnancy-related inhibition of hepatic drug metabolism. Both progesterone and estradiol are competitive inhibitors of microsomal oxidases in the liver (12). Hepatic drug elimination may also be impaired by estrogen-induced cholestasis (13). A reduction in Cl during pregnancy has been reported for other drugs, such as caffeine, and, most recently, ritodrine (14,15). In contrast to ropivacaine, lidocaine clearance was enhanced during pregnancy (3,4). The difference between the two local anesthetics may be related to the higher intrinsic hepatic extraction ratio for lidocaine (16). This may make lidocaine clearance more sensitive to increases in hepatic blood flow observed during the ovine pregnancy (17).

As with ropivacaine, no significant change in $t_{1/2\beta}$ of lidocaine was observed between pregnant and

Table 1. Mean Arterial Blood Pressure (mm Hg), Heart Rate (beats/min), Blood pH, and Gas Tensions (mm Hg) Before and at the End of Infusion, and 5 and 60 min Thereafter

	Before	End	End + 5 min	End + 60 min
Nonpregnant				
MABP	96 ± 5	109 ± 6	92 ± 5	86 ± 4
HR	92 ± 6	115 ± 9	105 ± 6	101 ± 6
pH	7.46 ± 0.02	7.50 ± 0.02	7.49 ± 0.02	7.51 ± 0.03
Pco_2	34 ± 2	31 ± 1	31 ± 1	33 ± 1
Po_2	87 ± 4	85 ± 3	81 ± 4	87 ± 5
Pregnant				
MABP	94 ± 3	106 ± 5	102 ± 4	92 ± 3
HR	108 ± 4	101 ± 4	105 ± 4	103 ± 3
pH	7.53 ± 0.01	7.55 ± 0.01	7.55 ± 0.01	7.53 ± 0.01
Pco_2	31 ± 1	28 ± 1	28 ± 1	32 ± 2
Po_2	89 ± 8	81 ± 3	82 ± 3	85 ± 5
Fetuses				
MABP	41 ± 4	43 ± 5	38 ± 3	36 ± 5
HR	148 ± 4	139 ± 8	136 ± 5	143 ± 3
pH	7.39 ± 0.02	7.39 ± 0.02	7.39 ± 0.02	7.39 ± 0.02
Pco_2	42 ± 2	43 ± 1	45 ± 2	41 ± 1
Po_2	22 ± 2	20 ± 1	20 ± 2	21 ± 1

MABP, mean arterial blood pressure; HR, heart rate.
Differences not significant. Values are mean ± SE.

Table 2. Derived Pharmacokinetic Indices

	Nonpregnant (n = 9)	Pregnant (n = 8)
$t_{1/2\alpha}$ (min)	3.3 ± 0.7	2.7 ± 1.1
$t_{1/2\beta}$ (min)	64.4 ± 7.4	74.7 ± 10.7
Vc (L/kg)	0.68 ± 0.08	0.41 ± 0.11
Vd_β (L/kg)	4.32 ± 1.03	2.03 ± 0.36
Vd_{ss} (L/kg)	2.96 ± 0.55	1.69 ± 0.27
Cl (mL·min^{-1}·kg^{-1})	45.1 ± 6.7	21.6 ± 4.5[a]
K_{12}	0.218 ± 0.062	0.513 ± 0.172
K_{21}	0.055 ± 0.011	0.084 ± 0.016
K_{10}	0.077 ± 0.016	0.067 ± 0.011

Values are mean ± SEM. See text for abbreviations.
[a]Significantly different from nonpregnant.

Table 3. Total Urinary Excretion of Unchanged Ropivacaine

	Nonpregnant (n = 6)	Pregnant (n = 7)
Dose (mg)	163 ± 12.0	188 ± 8.0
Dose (mg/kg)	2.85 ± 0.13	2.86 ± 0.09
Total urinary excretion (mg)	0.53 ± 0.13	0.19 ± 0.05[a]
Percentage of administered dose recovered	0.36 ± 0.10	0.10 ± 0.02[a]

Values are mean ± SEM.
[a]Significantly different from nonpregnant.

nonpregnant animals. In contrast, Vd_{ss} and Vd_β for lidocaine were higher during pregnancy in sheep (3,4). The reason for this difference between ropivacaine and lidocaine is not quite clear. Ropivacaine, being more lipid-soluble and protein-bound, may have a greater affinity for extravascular tissue binding sites also occupied by steroidal hormones of pregnancy. Competition between these hormones and oxyphenobutazone, an antiinflammatory drug, has been demonstrated (18). A smaller volume of distribution during pregnancy has also been noted for ritodrine (15).

A greater amount of unmetabolized ropivacaine was recovered in the urine of nonpregnant animals. However, the overall urinary elimination of the parent compound was so small, as was the case for lidocaine in our previous study (4), that the contribution of urinary clearance of ropivacaine to Cl was minimal in both groups of animals.

Placental transfer of ropivacaine occurred rapidly, the peak fetal plasma concentrations being measured 1–2 min after the end of maternal infusion. The adult and fetal plasma levels reached in this study did not result in any deterioration in heart rate, blood pressure, pH, or blood gas tensions.

In general, the effects of pregnancy on drug pharmacokinetics are variable. For example, in a review of 20 drugs (19), seven showed significant increases and six significant decreases in $t_{1/2\beta}$ during pregnancy, whereas no significant effects were noted for the remaining seven drugs. It would seem, therefore, that the effects of pregnancy on the disposition of an individual drug cannot be predicted.

In conclusion, we have demonstrated that the pharmacokinetics of ropivacaine are altered by ovine pregnancy. If the data obtained in this study are applicable to humans, an inadvertent intravascular injection of ropivacaine may result in higher plasma drug levels in the pregnant than the nonpregnant patient, but they would dissipate at similar rates.

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Effects of Thiobarbiturates on Smooth Muscle Reactivity in Isolated Aortas From Spontaneously Hypertensive Rats

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NAKAMURA K, HATANO Y, NISHIWADA M, YAKUSHIJI T, PARK JW. MORI K. Effects of thiobarbiturates on smooth muscle reactivity in isolated aortas from spontaneously hypertensive rats. Anesth Analg 1990;70:267–74.

The direct effects of thiobarbiturates on helical strips of aortas from spontaneously hypertensive (SH) rats were compared with those from Wistar-Kyoto (WKY) rats. At 5–6 wk of age, the arterial pressure of SH and WKY rats did not differ, and the effects of thiobarbiturates on aortic strips from SH and WKY rats were similar. By contrast, at the age of 10–12 or 20–21 wk arterial pressure was higher in SH than in WKY rats, and responses to thiobarbiturates differed in aortic strips from SH and WKY rats: contractile responses were greater in WKY than in SH rats, and relaxing effects were greater in SH than in WKY rats. Responses to sodium nitroprusside did not differ in the aortas of SH and WKY rats, but the effects of nifedipine were greater in strips from SH rats than from WKY rats at the age of 10–12 wk. Ca^{2+}-induced contractions of strips exposed to Ca^{2+}-free media and depolarized by high K^+ were inhibited by treatment with thiamylal; the inhibition was greater in SH than in WKY rats. The increase in smooth-muscle relaxation induced by thiobarbiturates in strips from SH rats may be due to increased sensitivity to the Ca^{2+}-channel blocking action of thiobarbiturates.

Key Words: ANESTHETICS, INTRAVENOUS—thiamylal, thiopental. MUSCLE, SMOOTH—responses to barbiturates. ARTERIES—responses to barbiturates.

It is clinically recognized that a marked reduction in systemic arterial pressure frequently occurs after induction of anesthesia with the intravenous administration of barbiturates in hypertensive patients (1). Prys-Roberts et al. (2) demonstrated that, in association with a decrease in arterial pressure after administration of thiopental, systemic vascular resistance is profoundly reduced in hypertensive patients but not significantly altered in normotensive patients. In vitro studies suggest that thiobarbiturates have both relaxing and constricting effects on isolated aortas of rats (3) and rabbits (4,5), on canine peripheral arteries (6), and on human cerebral arteries (7). Thus it seems possible that the sensitivities of the arterial vessels of hypertensive patients to thiobarbiturates may differ from those of normotensive patients. The spontaneously hypertensive (SH) rat, a strain established by Okamoto and Aoki (8), is accepted as an animal model of human essential hypertension (9,10). The present study compares the direct effects of barbiturates on isolated thoracic aortas from SH rats and, as a normotensive control, from Wistar-Kyoto (WKY) rats, the strain of rats from which the SH rat strain was derived.

Materials and Methods

The protocol was approved by the Kyoto University Animal Use Committee. Experiments were performed at the ages of 4–6 wk, 10–12 wk, and 20–21 wk in male SH or WKY rats obtained from Hoshino Farms of Experimental Animals (Saitama, Japan). After being anesthetized by intraperitoneal injection of 50 mg/kg of sodium pentobarbital, the rats underwent cannulation of a carotid artery for arterial pressure measurements, after which they were killed by exsanguination and their chests were opened for removal of the descending thoracic aortas. The aortas were then cut into helical strips approximately 17 mm long; each specimen was vertically fixed between hooks in an organ bath of 10-mL capacity, containing Krebs' bicarbonate solution (in mM: NaCl 118.2, KCl

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4.6, $CaCl_2$ 2.5, KH_2PO_4 1.2, $MgSO_4$ 1.2, $NaHCO_3$ 24.8, dextrose 10), which was maintained at 37° ± 0.5°C and aerated with a mixture of 95% O_2 and 5% CO_2. The pH of the solution was 7.40 ± 0.05. Hooks anchoring the upper end of the strips were connected to the lever of a force-displacement transducer (Toyo Baldwin T7-240, Japan), and the change in isometric tension was displayed on an ink-writing oscillograph (Rectigraph 8K, Nihondenki Sanei Co., Japan).

Before the start of experiments, resting tensions were adjusted to 1.0 g, and preparations were allowed to equilibrate for 90–120 min in the control media, during which time the bathing fluids were replaced every 10–15 min. The contractile response to 30 mM KCl was then measured, after which the preparations were washed three times with fresh media. For evaluation of the contracting effects of barbiturates under resting tension, barbiturates were then added directly to the bathing media in cumulative concentrations, and the changes in tension were expressed as the percent of the contractions induced by 30 mM KCl (which was taken to be 100%).

For evaluation of the relaxing effects, contractions in a range between 30% and 70% of those induced by 30 mM KCl were produced by KCl (20 mM) or phenylephrine (3×10^{-8}–2×10^{-7} M), and, after tension was stabilized, barbiturates or sodium nitroprusside were added to the bath in cumulative concentrations. At the conclusion of the relaxation studies, 10^{-4} M papaverine was added to produce the maximal relaxation, and the changes in tension induced by barbiturates or sodium nitroprisside were expressed as the percent of maximal (100%) relaxation induced by 10^{-4} M papaverine. The relaxation studies of barbiturates were performed in WKY and SH rats at the ages of 5–6 wk and 10–12 wk, as preliminary studies showed no significant differences in responses to barbiturates in 10–12-wk-old and in 20–21-wk-old rats of either strain (data not shown). In some aortic strips from SH and WKY rats, the endothelium was removed by gently rubbing the intimal surface with a cotton pellet; endothelial denudation was considered complete when acetylcholine (10^{-6} M)-induced relaxation was abolished.

For the studies of the effects of thiamylal on the Ca^{2+}-induced contraction, pairs of aortic strips were obtained from WKY or SH rats at the age of 10–12 wk. After the responses to 20 mM KCl had been measured in normal media, the preparations were exposed to Ca^{2+}-free media containing 0.1 mM ethyleneglycol-*bis*-*N*,*N*′-tetraacetic acid for 60 min, during which time the fluids in the bath were replaced every 20 min. After a 60-min exposure, one of the paired strips was exposed to 3×10^{-4} M thiamylal and the other to an equal volume of distilled water for control study. After another 10 min (i.e., after 70 min of exposure to Ca^{2+}-free media), 20 mM KCl was added to the bathing media. After yet another 10 min, the dose responses to Ca^{2+} (0.5–10 mM) were measured. The differences in Ca^{2+}-induced contractions between control and thiamylal-treated preparations or between WKY and SH strains were analyzed by Student's *t*-test for paired data.

To compare the effects of an inhibitor on the contractile response in aortas of SH and WKY rats, the isolated aortic strips were bathed for 20 min with the inhibitor before the contractile response to agonists was determined. Drugs used were thiopental sodium (Tanabe Pharmaceutical Co., Osaka, Japan), thiamylal sodium (Kyorin Pharmaceutical Co., Tokyo, Japan), L-phenylephrine hydrochloride (Sigma), sodium nitroprusside (Nacalai Tesque, Kyoto, Japan), and nifedipine (Bayer). All except nifedipine were dissolved in distilled water; nifedipine was dissolved in ethanol, the final concentration of ethanol being less than 0.01%. The solution of nifedipine and the organ bath used in experiments with nifedipine were covered with black paper to avoid light-induced breakdown of the drug.

Values are expressed as mean ± SEM. Student's *t*-test for paired data was used to analyze the effect of thiamylal on Ca^{2+}-induced contractions and the effect of nifedipine on KCl-induced contractions. Other data were analyzed statistically by Student's *t*-test for unpaired data. *P* values less than 0.05 were considered statistically significant.

Results

The body weights of WKY and SH rats averaged 122 ± 7 and 125 ± 6 g ($n = 6$, each group) at 5–6 wk of age, 233 ± 9 and 229 ± 7 g ($n = 8$, each group) at 10–12 wk, and 349 ± 6 and 317 ± 8 g ($n = 8$, each group) at 20–21 wk.

Mean Arterial Pressure

The mean arterial pressures of WKY and SH rats used in the experiments are shown in Table 1. At the age of 5–6 wk, mean arterial pressure did not differ significantly in the two strains of rats, but after the age of 10 wk the pressure was significantly higher in SH than in WKY rats.

Response to K^+ and Phenylephrine

There was no significant difference in the response to 30 mM KCl of the aortic strips from WKY and SH rats

Table 1. Mean Arterial Pressure (mm Hg) at Different Ages in Normotensive Wistar-Kyoto rats (WKY) and Spontaneously Hypertensive Rats (SHR)

5–6 wk		10–12 wk		20–21 wk	
WKY	SHR	WKY	SHR	WKY	SHR
77.5 ± 8.1 (n = 6)	83.0 ± 5.1 (n = 6)	76.0 ± 2.8 (n = 8)	132.5 ± 5.8[a] (n = 8)	85.7 ± 5.0 (n = 8)	136.7 ± 6.5[a] (n = 8)

Data shown are mean ± SEM. Figures in parentheses indicate the number of animals studied. [a] $P < 0.001$, significantly different between the two strains within the same age group.

Table 2. Contractions (mg) Induced by 30 mM KCl in Aortic Strips From Wistar-Kyoto Rats (WKY) and Spontaneously Hypertensive Rats (SHR) at the Ages of 5–6, 10–12, and 20–21 wk

5–6 wk		10–12 wk		20–21 wk	
WKY	SHR	WKY	SHR	WKY	SHR
397 ± 25 (n = 18)	414 ± 19 (n = 18)	530 ± 25 (n = 25)	547 ± 28 (n = 25)	464 ± 26 (n = 20)	515 ± 35 (n = 20)

Data shown are mean ± SEM. Figures in parentheses indicate the number of preparations studied.

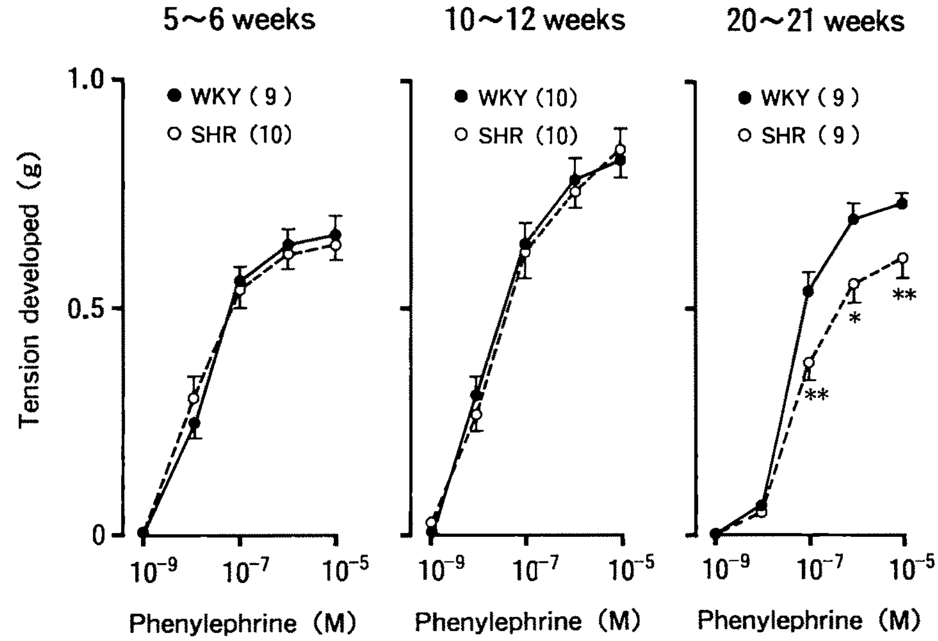

Figure 1. Dose-contractile response curves for phenylephrine in aortic strips from WKY and SH rats aged 5–6, 10–12, and 20–23 wk. Figures in parentheses indicate the number of preparations studied. *$P < 0.05$, **$P < 0.01$, WKY vs SH rats.

in any age group (Table 2). Responses of strips from WKY and SH rats to phenylephrine did not significantly differ at the age of 4–6 wk and 10–12 wk, but at the age of 20–21 wk they were significantly greater in WKY than in SH rats (Figure 1).

Responses to Barbiturates in Preparations With Resting Tension

Thiamylal and thiopental in concentrations of 3 × 10^{-5} to 10^{-3} M produced dose-dependent contractions in all aortic strips from WKY and SH rats at all ages. Dose-contractile response curves for thiamylal and thiopental in aortas from WKY and SH rats at the age of 5–6 wk, 10–12 wk, and 20–21 wk are shown in Figures 2 and 3. The contractile responses to thiamylal or thiopental were significantly greater in aortas from 10–12-wk-old or 20–21-wk-old WKY rats than in aortas from age-matched SH rats.

Responses to Barbiturates in Preparations Contracted With Phenylephrine or KCl

In the aortic strips from 5–6-wk-old WKY and SH rats previously contracted with phenylephrine, thiamylal

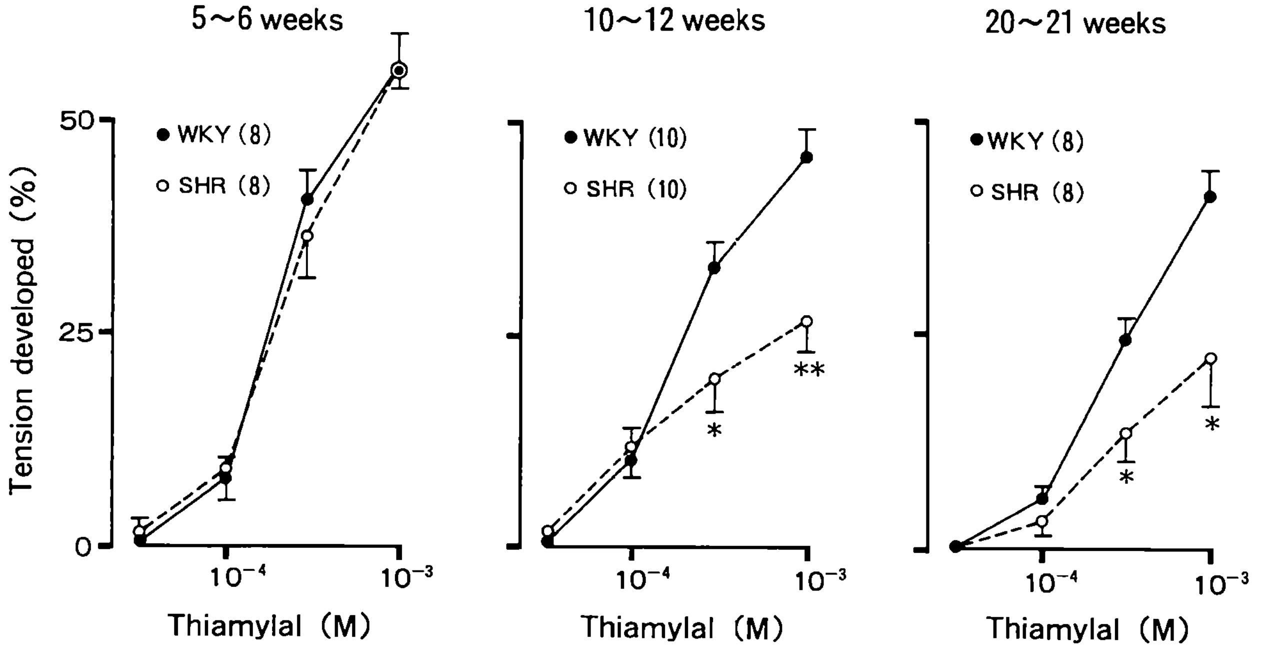

Figure 2. Dose-contractile response curves for thiamylal in aortic strips from WKY and SH rats aged 5–6, 10–12, and 20–21 wk. Contraction induced by 30 mM KCl was taken as 100%; mean absolute values in WKY and SH rats were 420 ± 42 and 394 ± 29 mg ($n = 8$, each group) at 5–6 wk, 496 ± 31 and 541 ± 69 mg ($n = 10$, each group) at 10–12 wk, and 508 ± 50 and 455 ± 58 mg ($n = 8$, each group) at 20–21 wk, respectively. Figures in parentheses indicate the number of preparations studied. $^*P < 0.05$, $^{**}P < 0.01$, WKY vs SH rats.

and thiopental in concentrations of 3×10^{-5} to 10^{-3} M caused a dose-related relaxation, which did not differ between aortas from WKY and SH rats (Figure 4, left; Figure 5, left). In the strips from 10–12-wk-old WKY rats previously contracted with phenylephrine, thiamylal and thiopental in low concentrations (3×10^{-5} to 10^{-4} M of thiamylal and 10^{-5} M of thiopental) caused contraction and in high concentrations (10^{-3} M) relaxation, whereas in aortas from SH rats they caused less contraction, with relaxation being the major response. At a higher concentration (10^{-3} M) barbiturates relaxed preparations from both strains to the same extent (Figure 4, right; Figure 5, right). Typical recordings of the responses to thiamylal of aortic strips from 10–12-wk-old WKY and SH rats are shown in Figure 6. The preparations contracted with KCl were relaxed by thiamylal or thiopental in a dose-dependent manner, and the relaxation was significantly greater in 10–12-wk-old SH rats than in age-matched WKY rats (Figure 7), but the responses did not differ in SH and WKY rats at 5–6 wk of age. Barbiturate-induced relaxation was significantly greater in aortic strips from 10–12-wk-old SH rats contracted with KCl than in those contracted with phenylephrine. The relaxing effects of sodium nitroprusside in phenylephrine-contracted aortic strips from SH and WKY rats did not significantly differ at the ages of 10–12 and 20–21 wk. The effects of barbiturates were not significantly altered by denuding endothelium from aortic strips of either strain.

Effect of Thiamylal on Ca^{2+}-Induced Contraction

In aortic strips exposed to Ca^{2+}-free media for 60 min, the addition of KCl did not produce any contraction. Reintroduction of Ca^{2+} produced contractions, and, as shown in Figure 8, the control dose-response curves for Ca^{2+} were not significantly different in two strains. Pretreatment with 3×10^{-4} M thiamylal shifted the dose-response curves to the right and downwards in both strains, the inhibitory effect of thiamylal being significantly greater in SH than in WKY rat aortas.

Effects of Nifedipine on the KCl-Induced Contraction

Contractions induced by 20 mM KCl in aortic strips from 10–12-wk-old WKY and SH rats, which averaged 96.8 ± 3.5 mg ($n = 7$) and 91.8 ± 14.3 mg ($n = 7$), respectively, were inhibited by nifedipine at 2×10^{-9} M to 65% ± 6% and 48% ± 8% ($n = 5$, each group), at 10^{-8} M to 31% ± 4% and 22% ± 2% ($n = 5$, each group), and at 5×10^{-8} M to 12% ± 3% and 10% ± 1% ($n = 6$, each group), respectively. The

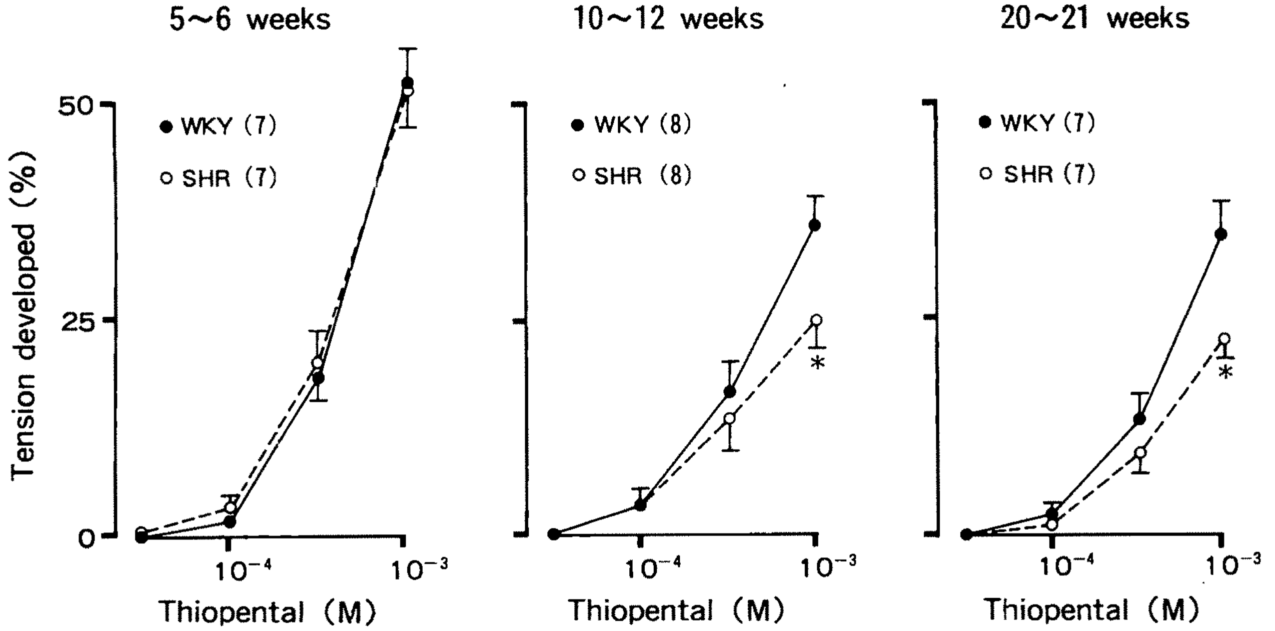

Figure 3. Dose-contractile response curves for thiopental in aortic strips from WKY and SH rats aged 5–6, 10–12, and 20–21 wk. Contraction induced by 30 mM KCl was taken as 100%; mean absolute values in WKY and SH rats were 420 ± 42 and 394 ± 29 mg ($n = 7$, each group) at 5–6 wk, 496 ± 31 and 541 ± 69 mg ($n = 8$, each group) at 10–12 wk, and 483 ± 48 and 554 ± 58 mg ($n = 7$, each group) at 20–21 wk, respectively. Figures in parentheses indicate the number of preparations studied. $^{*}P < 0.05$, WKY vs SH rats.

inhibition by nifedipine at concentrations of 2×10^{-9} M and 10^{-8} M was significantly greater in aortas from SH rats than it was in aortas from WKY rats ($P < 0.05$; Student's t-test for paired data).

Discussion

Under resting tension, helical strips of aortas from WKY and SH rats were contracted by thiamylal and thiopental in a dose-dependent manner, but when the strips were previously contracted with KCl or phenylephrine, both thiamylal and thiopental produced only a slight contraction in low concentrations and profound relaxation in high concentrations. Altura and Altura (3) demonstrated that thiopental has a direct vasoconstrictor effect as well as an inhibitory effect on K^+ or epinephrine-induced contraction in isolated rat aortas, and our findings are in agreement with theirs.

Mean arterial pressures of SH and WKY rats used in the present experiments did not differ significantly at the age of 5–6 wk, but the pressure in our SH rats was significantly higher than that in WKY rats at 10–12 wk and at 20–21 wk; this has also been reported

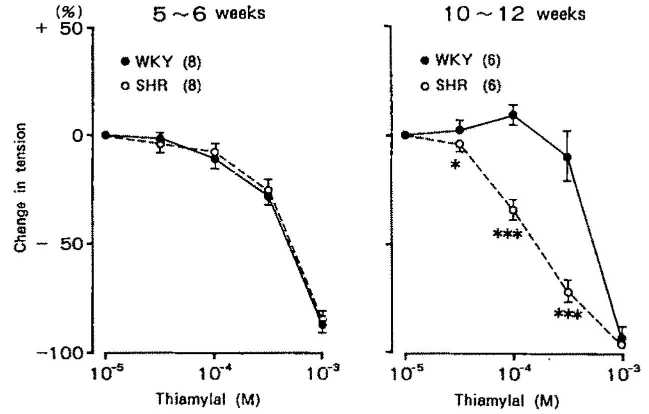

Figure 4. Responses to thiamylal in phenylephrine-contracted aortic strips from WKY and SH rats aged 5–6 and 10–12 wk. The absolute value of relaxation induced by 10^{-4} M papaverine was taken as 100%; mean values in WKY and SH rats were 485 ± 34 and 544 ± 44 mg ($n = 8$, each group) at 5–6 wk, and 487 ± 59 and 590 ± 66 mg ($n = 6$, each group) at 10–12 wk, respectively. Figures in parentheses indicate the number of preparations studied. $^{*}P < 0.05$, $^{***}P < 0.01$, WKY vs SH rats.

by others (8–13). Responses of aortic strips from SH rats and age-matched WKY rats to KCl, phenylephrine, or sodium nitroprusside did not differ significantly at any age with the exception of the responses to phenylephrine at the age of 20–21 wk. In contrast, responses to thiobarbiturates differed in aortic strips from SH rats and those from WKY rats at the age of 10–12 wk and 20–21 wk but did not differ at 5–6 wk.

In SH rats structural changes appear in arterial resistance vessels even before hypertension develops, changes that may themselves contribute to the development of hypertension (11,14). In contrast, structural changes in larger arteries, including the

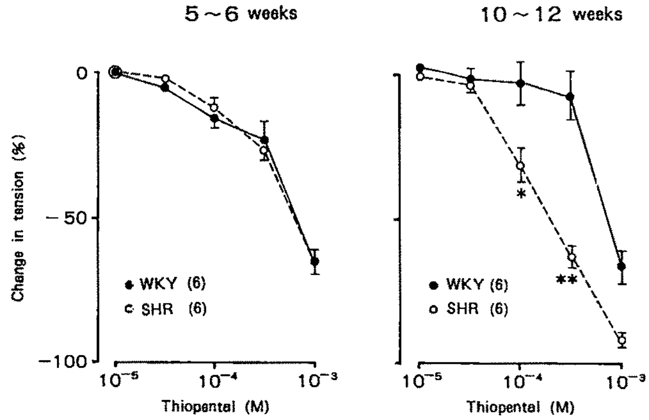

Figure 5. Responses to thiopental in phenylephrine-contracted aortic strips from WKY and SH rats aged 5–6 and 10–12 wk. The absolute value of relaxation induced by 10^{-4} M papaverine was taken as 100%; mean values in WKY and SH rats were, respectively, 470 ± 56 ($n = 6$) and 492 ± 37 mg ($n = 6$) at 5–6 wk and 368 ± 45 ($n = 6$) and 516 ± 50 mg ($n = 6$) at 10–12 wk. Figures in parentheses indicate the number of preparations studied. *$P < 0.05$, **$P < 0.01$, WKY vs SH rats.

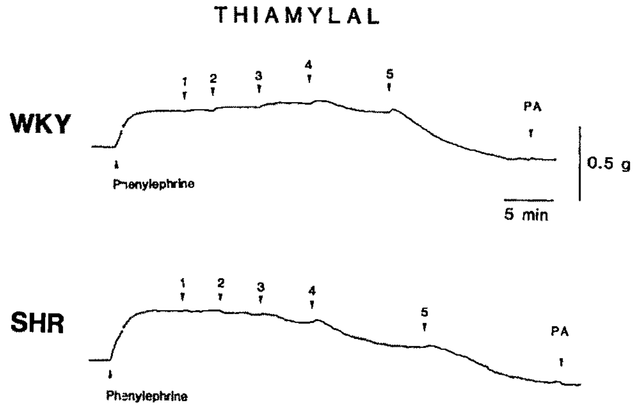

Figure 6. Comparison of the responses to thiamylal of aortic strips from WKY (*upper tracing*) and SH (*lower tracing*) rats aged 10–12 wk previously contracted with phenylephrine. 1, 2, 3, 4, and 5 represent thiamylal in the concentration of 10^{-5} M, 3×10^{-5} M, 10^{-4} M, 3×10^{-4} M, and 10^{-3} M, respectively. PA represents 10^{-4} M papaverine.

aorta, are not observed in SH rats at approximately 1 mo of age, and the hypertrophy of smooth-muscle cells and other morphologic changes in aortas observed at the age of 10 wk or older are considered to be secondary adaptive changes (11,15). Alterations in Ca^{2+} dynamics have been observed in smooth-muscle cells of thoracic aortas from SH rats at 8–12 wk, but not in aortas from SH rats at 4 wk (12). The fact that responses to thiobarbiturates in the present study did not differ in aortic strips from SH rats in the prehypertensive stage suggests that the difference in responses to barbiturates observed in SH rats at 10 wk or beyond are not derived from genetic differences but probably related to the early secondary changes in the aorta caused by hypertension (11,13).

Several in vivo and in vitro studies have suggested greater susceptibility of SH than normotensive rats to Ca-channel blockers such as diltiazem or nifedipine (16–18). Flaim et al. (16) found that diltiazem decreased arterial pressure and systemic vascular resistance more in SH than in WKY rats. Pederson and associates (18) showed that vascular smooth-muscle cells of aortas from SH rats are more sensitive to the effect of nifedipine than the aortas from control rats. Our findings that KCl-induced contractions were attenuated by nifedipine to a greater extent in SH than in WKY rats is in agreement with their observations.

On the other hand, it has been suggested that barbiturates, including thiopental, have Ca-channel blocking action in rat aortas (3) and in human cerebral arteries (7). It is known that KCl-induced contraction of vascular smooth muscle is more dependent on extracellular Ca^{2+} and therefore more sensitive to Ca-channel blockers than is phenylephrine-induced contraction (19). Accordingly, the present finding that the relaxing effects of thiobarbiturates were greater in aortic strips contracted by KCl than aortic strips contracted by phenylephrine also support Ca-channel blocking action of thiobarbiturates.

In the present study, thiobarbiturates induced greater relaxation in KCl-contracted strips from SH rats than they did in those from WKY rats at 10 wk or more. The Ca^{2+}-induced contraction of the strips exposed to Ca^{2+}-free media and depolarized by high K^+ was attenuated by thiamylal, and the attenuation was greater in aortic strips from SH rats than those from WKY rats at the age of 10–12 wk. Thus it seems likely that the aortas from SH rats are more susceptible to the Ca-channel blocking action of thiobarbiturates than are those from WKY rats.

Greater relaxation was induced by thiobarbiturates in phenylephrine-contracted aortic strips from SH than from WKY rats. Folkow et al. (20) observed that the contractions of the resistance vessels in SH rats by vasoconstrictors such as norepinephrine are more dependent on external Ca^{2+} than are the contractions in control rats. Zsoter et al. (21) suggested that Ca^{2+} availability from intracellular storage sites is lower in vascular smooth muscle from aortas from SH rats, and this may explain the greater sensitivity to barbiturates in the relaxation of phenylephrine-contracted aortas from SH than from WKY rats.

In addition to the differences in sensitivity to the relaxing effects of thiobarbiturates, aortic strips from SH and WKY rats appear to have different sensitivities to the constrictor effects of thiobarbiturates. Our previous study with canine peripheral arteries (6) revealed that the contraction induced by thiobarbitu-

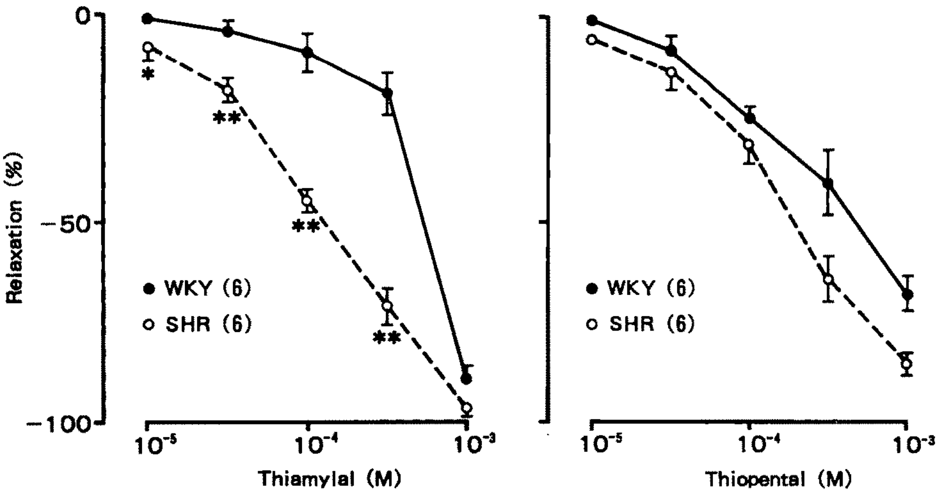

Figure 7. Responses to thiamylal and thiopental of aortic strips from WKY and SH rats aged 10–12 wk previously contracted with KCl (10 mM). The absolute value of relaxation induced by 10^{-4} M papaverine was taken as 100%; mean values for thiamylal in strips from WKY and SH rats were 407 ± 9 ($n = 6$) and 442 ± 67 mg ($n = 6$), respectively, and those for thiopental 315 ± 6 ($n = 6$) and 490 ± 90 mg ($n = 6$), respectively. Figures in parentheses indicate the number of preparations studied. $*P < 0.05$, $**P < 0.01$, WKY vs SH rats.

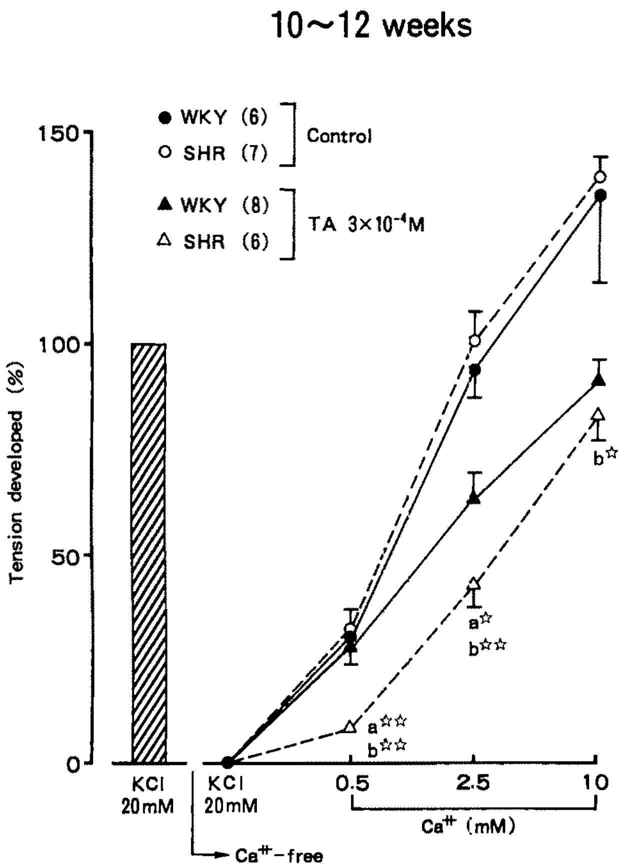

Figure 8. Modification by thiamylal of the contractile response to Ca^{2+} of aortic strips exposed to Ca^{2+}-free media and treated with KCl (20 mM). In the thiamylal-treated group, 3 × 10^{-4} M thiamylal was given 20 min before addition of KCl in Ca^{2+}-free media. TA: thiamylal. Figures in parentheses indicate the number of preparations studied. a☆: $P < 0.05$, a☆☆: $P < 0.01$, WKY vs SH rats; b☆: $P < 0.05$, b☆☆: $P < 0.01$, control vs thiamylal-treated rats.

rates is mainly associated with Ca^{2+} influx from extracellular fluids and is inhibited by Ca-channel blockers such as nifedipine or diltiazem. These findings suggest that thiobarbiturate-induced contraction caused mainly by Ca^{2+} influx is inhibited by Ca-channel blocking action at higher concentrations. The apparent difference in the vasoconstricting potency of thiobarbiturates in SH and WKY rats could be explained in part by the view that thiobarbiturates, as Ca-channel blockers, can attenuate the contraction they induce to a greater extent in aortic strips from SH rats than those from WKY rats.

The possibility that the mechanism underlying the different response to barbiturates of aortas from SH and WKY rats may involve the endothelium-dependent relaxation or contraction can be ruled out, as the removal of the endothelium did not alter the responses (22–24). However, thiobarbiturates might have intracellular effects resulting in relaxation in addition to their Ca-channel blocking action, and it may be possible that the potency of intracellular action of thiobarbiturates also differs in SH and WKY rats.

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Rate of Change of Somatosensory Evoked Potentials During Isoflurane Anesthesia in Newborn Piglets

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BOSTON JR, DAVIS PJ, BRANDOM BW, ROEBER CM. Rate of change of somatosensory evoked potentials during isoflurane anesthesia in newborn piglets. Anesth Analg 1990;70:275–83.

Most studies of the effects of inhalation anesthetics on somatosensory evoked potentials (SSEPs) have examined SSEP at single times after initiation of an anesthetic. This study describes SSEP changes as functions of time of exposure to isoflurane. Both transient and sustained SSEP changes were observed. Nonlinear regression was used to fit exponential terms to the trend curves for end-tidal anesthetic concentration and SSEP peak latency. End-tidal concentrations could be well described by two exponential terms, one with a long and one with a short time constant. Isoflurane at 1% inspired concentration produced a sustained SSEP latency change that could be fit by a single exponential term; the time constant was essentially identical to the long time constant of end-tidal concentration. The long time constants ranged from 7 to 33 min. At 0.5% isoflurane, SSEP changes were often small or not sustained, and the changes could not always be well described by an exponential curve. These data suggest that the time-course of anesthetic effects on SSEPs may be prolonged and complex, and the possibility of changes over time should be considered both in experimental studies and during intraoperative monitoring.

Key Words: BRAIN, EVOKED POTENTIALS. ANESTHETICS, VOLATILE—isoflurane.

Somatosensory evoked potentials (SSEPs) give information on the integrity of peripheral nerves, spinal cord, and brain structures and are routinely monitored during surgery involving instrumentation and fusion of the vertebral column or operations on the spinal cord. However, most drugs used to induce and maintain anesthesia have some effect on the SSEPs. Which anesthetic agents have the greatest effects on the SSEPs and which are most suitable for use with monitoring is not clear.

The effects of inhalation anesthetic agents on SSEP latencies and amplitudes have been particularly controversial. Several early reports described significant waveform alterations related to the use of halothane (1,2) and isoflurane (3). Grundy (4) recommended that halogenated agents be avoided when monitoring SSEPs; a combination of nitrous oxide and narcotics is commonly used. Several recent studies have described significant changes in amplitude and latency of cortical SSEPs during inhalation anesthesia in dogs (5) and humans (6–9).

On the other hand, several recent reports have suggested that SSEP monitoring is feasible with low concentrations of halogenated anesthetics and that the associated changes are smaller than those seen with nitrous oxide (10,11). Peterson et al. (12) studied the effects of halothane, enflurane, and isoflurane given in combination with 60% nitrous oxide on median nerve SSEPs in humans. The investigators were able to record responses in all subjects at 0.5, 1.0, and 1.5 MAC halothane, at all but 1.5 MAC isoflurane, and at only 0.5 MAC enflurane. However, the anesthetics induced a significant increase in latency and a substantial (>50%) decrease in amplitude. Wolfe and Drummond (13) obtained similar results with posterior tibial nerve stimulation and concluded that intraoperative monitoring with inhalation agents is feasible, although changes in anesthetic concentration would be expected to cause changes in the SSEP waveform.

In summary, at high concentrations inhalation anesthetics induce changes in response parameters

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that eventually lead to loss of the response and loss of ability to monitor. At low concentrations the response parameters are minimally affected, and monitoring may be possible. The sizes of the reported SSEP changes varied among the studies, however, possibly because the studies examined SSEPs obtained at single, fixed times (usually 15 or 30 min) after initiation of an anesthetic.

This study was undertaken to evaluate a technique to describe SSEP changes as functions of time after initiation of isoflurane anesthesia and to relate these time functions to changes in end-tidal anesthetic concentration over time. The study was carried out in newborn piglets. Infants are known to differ from adults in their responses to inhalation anesthetics in having—for example—higher MAC values (14). Evoked potential parameters also differ from adult values in having longer latencies and lower amplitudes (15). However, methods to describe changes in SSEPs related to duration of exposure to an inhalation anesthetic should be applicable in both cases, even though specific values of time constants might differ. The smaller animals provided a more convenient preparation with which to evaluate these measurement and analysis techniques than would adult animals.

Methods

The experimental protocol was approved by the Animal and Human Rights Committee of Children's Hospital of Pittsburgh. Piglets 4–14 days old were anesthetized with thiopental (20 mg/kg), after which metocurine was given to facilitate tracheal intubation. Ventilation was controlled with the use of a proximal inspiratory pressure of 20 cm H_2O, end-expiratory pressure of 2 cm H_2O, a respiratory rate appropriate to maintain normocapnea, and oxygen as a carrier gas. Local anesthesia was used to place catheters in the internal jugular vein and femoral arteries. Blood pressure was monitored using femoral artery catheters. Thermodilution cardiac output was measured by injection of 1.5-mL aliquots of cold saline solution (0°C) into the superior vena cava, with a thermistor in the descending aorta.

A time line for the protocol is shown in Figure 1. After induction, anesthesia was maintained in most animals with fentanyl and oxygen to provide a 60-min period for the effects of drugs given at intubation to diminish. In four animals, isoflurane was started 20 min after induction to avoid the administration of fentanyl. Except for the animals in which isoflurane was started immediately, animals received a 10-μg/kg bolus of fentanyl at 30 and 90 min after induction. Isoflurane was administered as a step change to 0.5% or 1% inspired concentration 30 min after the first fentanyl dose. Isoflurane was continued for 1 h and then terminated as a step decrease. Fentanyl doses were repeated in all animals 30 min after termination of isoflurane to ensure adequate anesthesia. A second administration of isoflurane was given 1 h after the first.

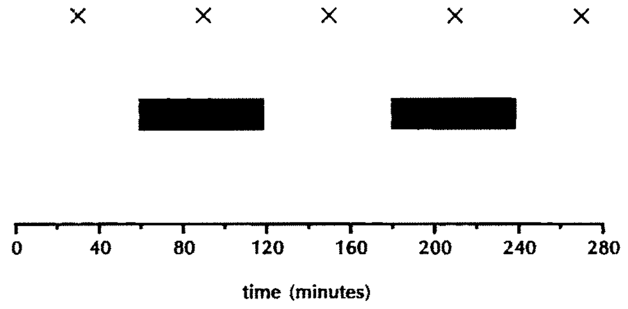

Figure 1. Time line for the experimental protocol after induction at time zero. Administration of inhalation anesthetic is shown by the *heavy bar*; × shows the bolus administration of fentanyl.

Response waveforms were recorded with needle electrodes at the vertex (positive) and on the forehead (negative) approximately 1 cm above the eyes. A ground electrode was placed behind the ear on the stimulated side. Nicolet amplifiers with gain of 50,000 and bandpass of 0.1–1500 Hz were used. Signal averaging and analysis were implemented on an IBM XT-286 computer. The stimulus trigger was generated by the computer after the beginning of the analysis window, yielding a prestimulus control interval of 30 ms and a poststimulus response interval of 80 ms. Two averaged waveforms were acquired simultaneously, with responses to even-numbered stimuli in one average and responses to odd-numbered stimuli in the second average (16). The two averages were combined for a total of 256 individual responses, and response peak amplitudes and latencies were measured with an interactive cursor on the waveform.

Expired concentrations of volatile anesthetic were continuously monitored using a Puritan-Bennett infrared gas analyzer. After acquisition of each evoked potential, 30 s of gas analyzer analog output was acquired by the computer, and maximum inspired and end-tidal concentrations were calculated. Inspired concentrations were used to estimate input concentration of anesthetic, and end-tidal concentrations were used to estimate arterial blood levels.

Somatosensory evoked potentials, blood pressure, and electroencephalographic waveforms were automatically acquired every 3 min throughout the experiment. Cardiac output and blood gas tensions were measured 5 min after each fentanyl bolus. Fluids

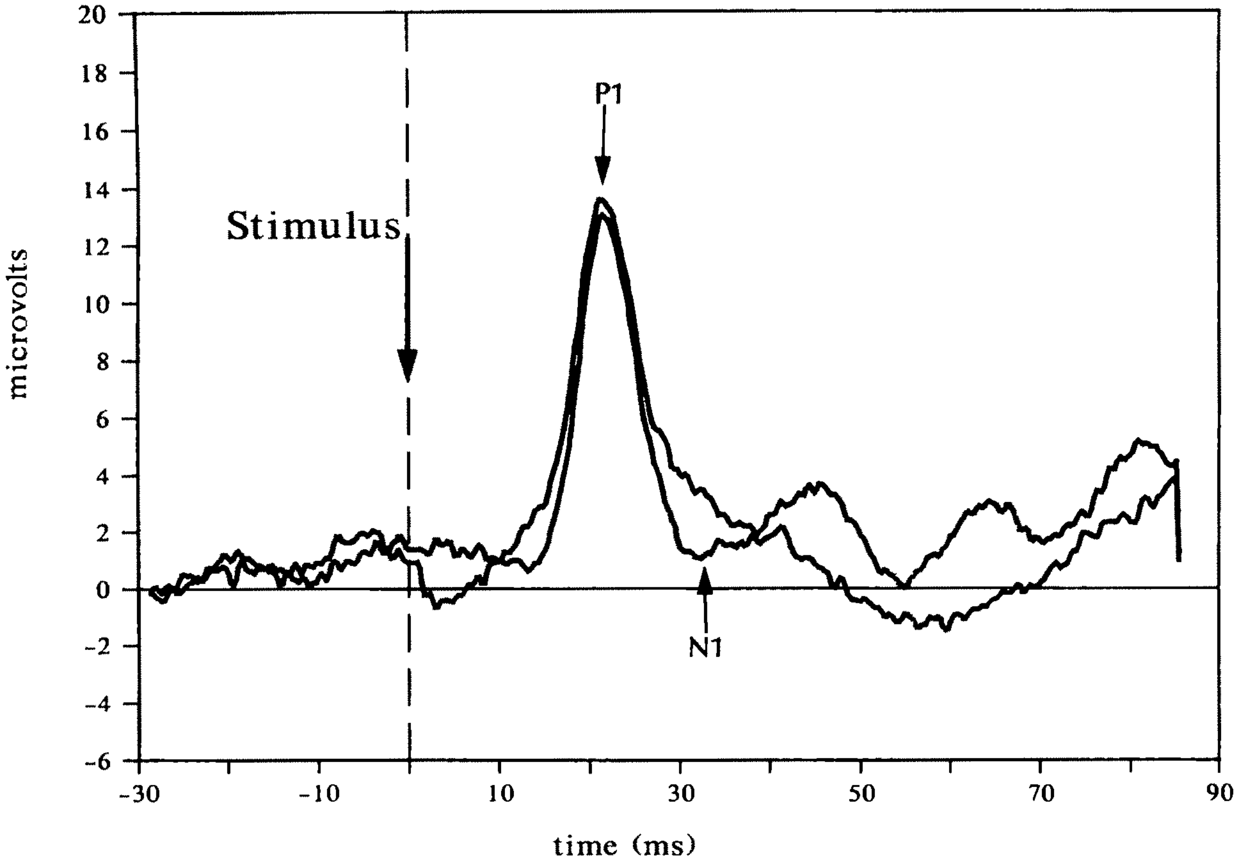

Figure 2. Typical piglet SSEP to forelimb stimulation, recorded between the vertex and forehead. P1 (the positive peak at a latency of approximately 20 ms) and the P1 to N1 amplitude were measured to characterize the waveform. (N1 is the trough following P1.)

were administered to maintain cardiac output and blood pressure within physiologic limits. Acid-base imbalance was treated by adjusting respiratory rate and/or by bicarbonate administration. A warming lamp was used to minimize changes in blood temperature. Additional arterial blood samples were drawn as necessary to verify maintenance of adequate acid-base balance and blood gas tension (no more than three additional samples per animal).

Trend plots for SSEP peak latency and end-tidal anesthetic concentration were examined. The trend plots were fit by nonlinear regression with quasi-Newton iteration (tolerance = 0.0001) to an equation of the form

$$y = y_o + K\,[1 - \exp(-t/a)],$$

where y_o represents the variable before isoflurane was administered, K represents the maximum latency change, t represents time in minutes, a is the time constant, and exp represents the exponential function. Goodness-of-fit was indicated by the regression analysis of variance, with $P < 0.01$ taken to indicate a satisfactory fit. R^2, the coefficient of determination, was also evaluated.

The statistical significance of differences in time constants among animals and between the latency and anesthetic time constants was examined by a multivariate linear regression after transformation of the latency and end-tidal concentration data. The transformation was

$$y = -\ln[(x - x_{max})/(x_o - x_{max})],$$

where y is the transformed variable, x is the measured SSEP latency or end-tidal concentration, x_o is the measured variable just before isoflurane was administered, and x_{max} is the maximum value of the variable measured while isoflurane was being administered. Applying this transformation to the equation given in the previous paragraph yields a variable that is linearly proportional to time, with constant of proportionality equal to $1/a$. Indicator variables for the individual animals were included, and the significance to the regression of the contribution of these variables as a single group was evaluated by comparing the residual sum-of-square errors with and without the group of indicator variables (17). An indicator variable to distinguish between latency and end-tidal data was included to test for significance of differences between these time constants. No weighting was used, and data obtained after the steady state was reached were excluded.

Results

An example of SSEP waveforms recorded in piglets is shown in Figure 2. The most prominent and consistent feature is the peak at approximately 20 ms, labeled P1. Several additional peaks and troughs were usually observed, but they were variable from animal to animal and did not show repeatable changes with anesthetics. In this study, only P1 latency and P1-N1 (peak-to-following trough) amplitude were analyzed.

A total of 18 isoflurane administrations in 10 animals were studied. Latency increases were consistently observed with both 0.5% and 1% inspired isoflurane concentrations. With the 1% level, these increases were large (>2 ms) and were sustained as long as the inhalation anesthetic was administered. For 0.5%, the initial changes were consistently greater than 1 ms, but they could be either transient or sustained.

Latency changes were classified as transient or sustained by measuring the return of latency toward the baseline value from the maximum latency observed during anesthesia. The relative latency recovery (r) was defined as

$$r = \frac{\text{Maximum change} - \text{Final change}}{\text{Maximum change}}$$

where the final change was the difference between latency measured just before termination of the anesthetic and the latency measured before initiation of the anesthetic. To distinguish between transient and sustained responses, the value of r was arbitrarily set at 0.5; for transient responses, $r \geq 0.5$. Table 1 shows the number of transient and sustained changes, the average maximum latency change, and the average recovery (r) for each anesthetic concentration.

Intravenous fentanyl did not always affect the SSEP, but the effect was rapid when it occurred. The change observed was usually a latency decrease (return toward preinhalation anesthetic baseline) rather than an increase. To quantify this effect, the latency of the SSEP obtained just after fentanyl administration was subtracted from the latency obtained just before fentanyl administration. The two SSEPs were obtained 6 min apart. Results are given in Table 1. Analysis of variance by anesthetic concentration with relative recovery as a covariate showed that the latency decrease associated with fentanyl was correlated with recovery ($P = 0.04$). That is, fentanyl administration produced a large latency decrease when recovery was large (transient response) and a small decrease when recovery was small (sustained response).

Table 1. Summary of Evoked Potential Changes for Different Isoflurane Concentrations

Response type	n	Maximum latency change	Relative recovery	Latency change with fentanyl
0.5% Isoflurane				
Without fentanyl				
Transient	1	0.6	1.00	—
Sustained	2	2.9 (0)[a]	0.26 (0.16)	—
With fentanyl				
Transient	6	2.1 (0.3)	0.93 (0.12)	−0.57 (0.36)
Sustained	3	1.5 (0.6)	0.12 (0.12)	0.00 (0.17)
1% Isoflurane				
Without fentanyl				
Transient	0	—	—	—
Sustained	1	3.4	0.15	—
With fentanyl				
Transient	0	—	—	—
Sustained	5	4.0 (0.5)	0.17 (0.06)	−0.12 (0.30)

[a] Standard errors are in parentheses.

All changes in latency with 1% isoflurane were sustained, and all but one could be well fit by a single exponential ($P < 0.01$). The one exception showed a reasonable fit ($P = 0.029$); peripheral SSEP responses were recorded in this animal, and substantially fewer data were available for the regression. Of the five sustained responses at 0.5% isoflurane, the maximum latency change in three was less than 2 ms; nonlinear regression for two of these did not converge, and the third yielded a regression analysis of variance with $P > 0.05$. The remaining two (one with fentanyl and one without) had maximum changes of greater than 2.5 ms, and both could be fit by a single exponential. Transient latency changes could not be fit because the latency returned to baseline before a steady changed value was reached.

During the experiments, the first inhalation anesthetic concentration waveform was not recorded from the gas analyzer until approximately 2 min after the anesthetic had been initiated. (During this time, the first SSEP was being acquired.) By this time, the end-tidal concentration was approximately 80% of inspired concentration. A slow exponential increase to the final value of end-tidal concentration occurred

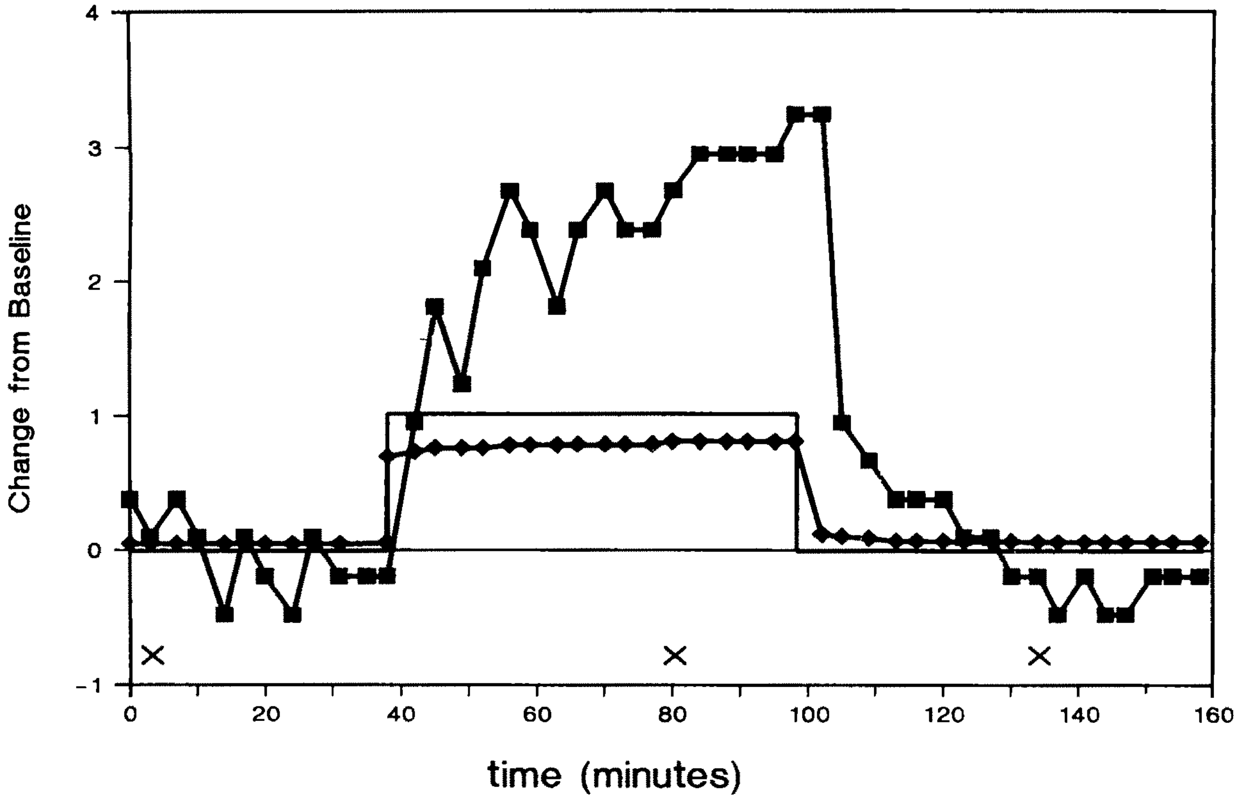

Figure 3. Example of sustained changes in P1 latency of 1% isoflurane. ■, P1 latency change (ms); —, inspired isoflurane concentration (%); ◆, end-tidal isoflurane concentration (%); ×, time of fentanyl dose.

over the next 60 min, as shown in Figures 3 and 4. These data could be well fit ($R^2 > 0.90$) by a single exponential curve if the first data point after the change in inhalation anesthetic concentration was the first point considered—that is, no attempt was made to force the curve to zero end-tidal concentration at time zero.

To make these curves consistent with the observed concentration data, we assumed that anesthetic uptake actually consisted of two exponentials: one with a short time constant and one with a long time constant. The short time constant, or fast component, was essentially over in 2 min, the time that the first anesthetic concentration was measured. Hence, the measured concentrations only reflected the long time constant, or slow component. The regression curves based on the measured concentrations will be referred to as the slow uptake component.

Table 2 summarizes the nonlinear regression results for each animal for which fits were obtained. The time constants for the exponentials that were fit to the slow component of end-tidal concentration were approximately equal to the time constants for the latency change. The time constants ranged from 7 to greater than 30 min. The linear multiple regression model using the transformed variables and the indicator variables gave similar values for time constants. Analysis of this model showed a significant difference among animals [F(7,126) = 16.8, $P < 0.01$] but no difference between latency and end-tidal concentration [F(1,123) = 3.2, $P = 0.16$].

An example of the agreement between the latency time constant and the slow component of the end-tidal concentration time constant is shown in Figure 4; the data in Figure 3 were divided by the maximum change between the first measurement point after initiation of isoflurane and the final value to normalize the changes to one. The normalized curves are very similar.

Somatosensory evoked potential amplitude (P1 to N1), electroencephalographic total power, and 90% spectral edge (frequency below which 90% of the electroencephalographic power resides) showed changes that were similar to P1 latency. However, these parameters were variable and did not yield good exponential fits. Data on blood temperature, pressure, heart rate, and blood gas tensions are summarized in Table 3. Multivariate analysis of variance showed no significant changes for any variable except mean arterial blood pressure. These variables were also examined for correlation with the time constants, but no significant correlations were found.

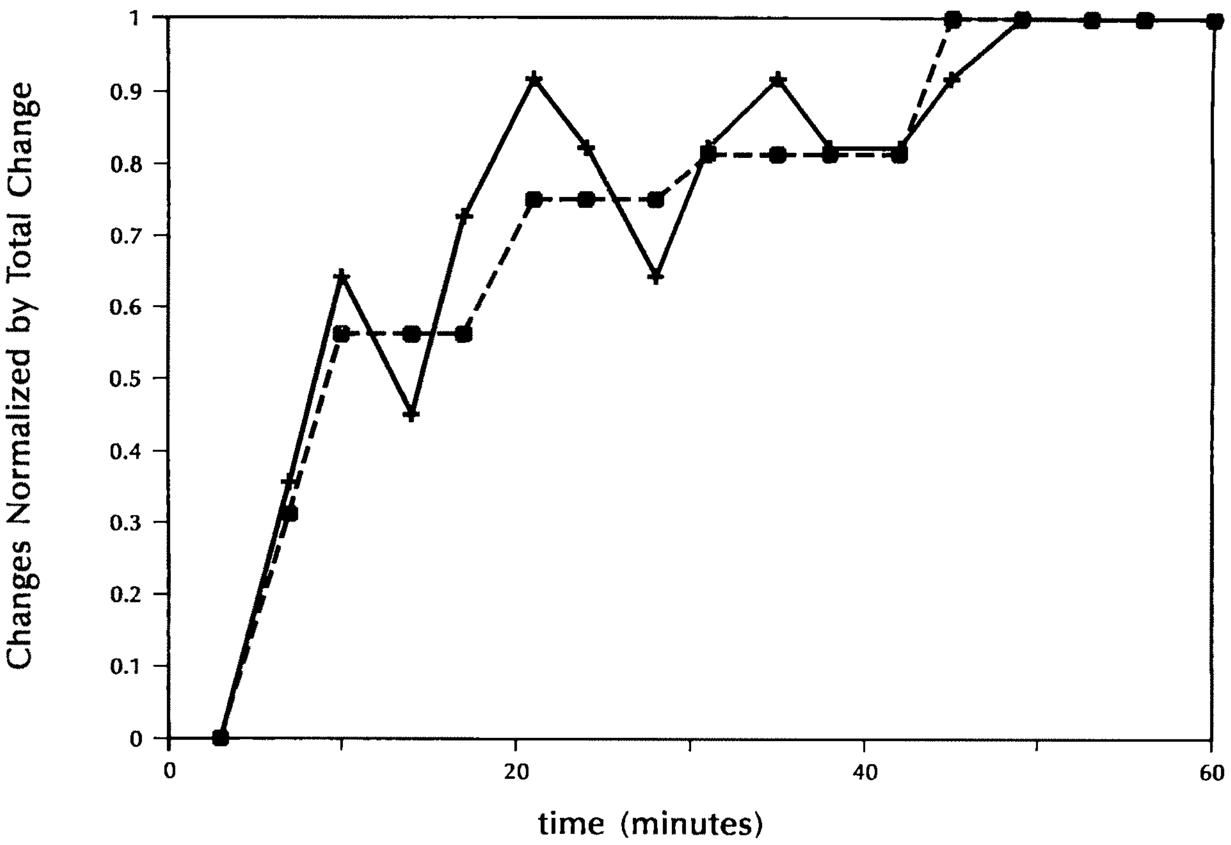

Figure 4. P1 latency and end-tidal isoflurane concentration data from Figure 2, normalized by the change in each parameter between the first measurement point after initiation of isoflurane and the final value. +, P1 latency change; ■, end-tidal isoflurane concentration change.

Discussion

Allison et al. (18) have argued that SSEPs in cats and rats show a positivity that corresponds to the negative peak at 20 ms in primates and reflects the initial activation of the somatosensory cortex. The peak P1 measured in this study may similarly represent early cortical activity. The long latency of this peak relative to the size of the animals may be due to the young age of the animals. The results obtained here show that sustained SSEP latency changes as a function of time after isoflurane in piglets can be well described by a single exponential. This time constant is essentially equal to the long time constant associated with change in end-tidal anesthetic concentration.

The largest recorded change in blood temperature (during 1% isoflurane) was 1.5°C. Several investigators have described changes in SSEP latency due to small temperature changes of 0.5–0.7 ms/°C (over the range of 34°–37°C) in humans (19,20). If these data can be extrapolated to newborn piglets, the maximum SSEP latency changes that would be expected because of temperature changes would be no larger than 1 ms, compared with the observed changes of 2–5 ms. Hence, it seems unlikely that temperature had a major effect on the observed latency changes.

Table 2. Time Constants in Minutes of Changes After Isoflurane

Inspired isoflurane concentration (%)	End-tidal concentration time constant	Latency change time constant
0.5	9.4	8.5
0.5	23	33
1	14	18
1	13	11
1	15	21
1	18	11
1	17	23
1	7.4	7.1[a]

[a] $R^2 = 0.83$. For all other regressions, $R^2 > 0.90$.

Mean arterial blood pressure did show significant decreases during inhalation anesthesia. Although mean blood pressures as low as 53 mm Hg were recorded during anesthesia, it seems unlikely that compromised cerebral perfusion was a significant contributor to the observed changes in SSEP. Electroencephalographic monitoring showed increases in amplitude and decreases in frequency during these

Table 3. Physiologic Parameters

	Blood temperature (°C)	Blood pH	Blood gases		Base excess	Cardiac output (L/min)	MAP (mm Hg)	Heart rate (beats/min)
			Po_2 (mm Hg)	Pco_2 (mm Hg)				
Parameters 30 min before initiation of inhalation anesthetic								
Average	37.41	7.38	373	41.3	−0.94	0.70	107	222
SE	0.09	0.02	12	2.7	0.50	0.08	3.3	9
n	18	16	16	16	16	15	18	18
Parameters 30 min after initiation of inhalation anesthetic								
Average	37.20	7.40	373	41.9	0.24	0.64	91[a]	204
SE	0.14	0.01	15	2.2	0.60	0.07	4.5	10
n	18	17	17	17	17	17	18	18

MAP, mean arterial pressure.
[a] Different from baseline ($t = 3.91$, df = 17, $P = 0.001$).

experiments but no changes associated with ischemia. Studies in adult baboons have shown that SSEPs are little affected until cerebral blood flows are below levels associated with ischemic changes in the electroencephalogram (21).

The time constants associated with SSEP latency changes showed unexpected variability, ranging from 7.1 to 33 min. The similarity between the time constants of the SSEP latency changes and those of the end-tidal anesthetic concentration changes suggests that the latency changes may be associated with the overall uptake of anesthesia by the brain. In other experiments, we have observed that anesthesia develops progressively over at least 25 min with 1% isoflurane in piglets. Hence, the time constants of SSEP changes may be consistent with the development of anesthetic effects.

These time constants were longer than would be expected for uptake of inhalation anesthetic by the brain in adult humans; Eger gives a value of 3.3 min for halothane, and isoflurane should be approximately the same, based on a similar tissue/blood partition coefficient (14). Part of the difference may be due to the fact that the present study in effect used a two-compartment model for analysis of anesthetic uptake; sufficient data were not available for more compartments. Carpenter et al. (22) reported anesthetic uptake data that could be fit with two or three compartments. When three compartments were used, the middle time constant, presumably associated with vessel-rich tissues, was 2–3 min. When two compartments were used, the longer time constant, presumably representing a combination of vessel-rich and other tissues, was 6–7 min. The latter values are at the small end of the range observed in this study.

The reasons for the significant variability of time constants among animals observed in this study are not clear. There was no correlation between end-tidal anesthetic time constant and respiratory rate, cardiac output, or mean blood pressure. However, cardiac output was only measured 30 min after initiation of the anesthetic; transient changes may have occurred before the cardiac output measurement was made. There was also no correlation between time constant and age or weight of the animals. The conclusion that the time constants were not correlated with these variables is tentative, however, because of the small number of animals for which adequate exponential fits were obtained.

These results do not indicate whether the effects of inhalation anesthetics occur in the peripheral or the central nervous system. Peripheral responses (above the spine at approximately Cv_2) can be recorded in piglets if a longer averaging time is used than that required for cortical responses. To obtain cortical data as rapidly as possible, peripheral responses were not routinely recorded in this study. However, peripheral responses were recorded in two animals that showed large sustained latency changes. Latency changes in the peripheral responses were less than 1 ms; most of the latency increase occurred between the peripheral and cortical response components, suggesting that the isoflurane effects are predominantly in the central nervous system.

Several reports (23–26) have described little or no effects of fentanyl on SSEP, and we were surprised that, in this study, fentanyl administration did affect SSEP latency during 0.5% isoflurane. The effect appeared to be related to whether the latency change was transient or sustained. For some transient changes, fentanyl administration was associated with the return of latency to the preinhalation anesthetic baseline. For other transient changes, the return of latency toward baseline had already begun when fentanyl was administered. Koht et al. (27) have also described a stabilizing effect of fentanyl; they observed that fentanyl diminished an amplitude-enhancing effect that was observed for etomidate.

For sustained responses fentanyl administration had little effect on latency. The animals did not show signs (for example, increased blood pressure) of inadequate anesthesia before fentanyl administration, and we can suggest no mechanism that would explain the differences.

Pathak et al. (28) reported a latency increase of several milliseconds in lower-extremity SSEP after fentanyl administration during intraoperative monitoring with nitrous oxide anesthesia. Measurements were made 30 and 150 min after fentanyl administration. Fentanyl dosage was not specified. It is not clear why these results are not consistent with those of other investigators and with the results in the present study. Pathak et al. were looking at lower-extremity responses, whereas the other studies considered median nerve responses. These procedures were for placement of Harrington rods; the spinal cord was exposed, and local cooling may have contributed to the changes. The long interval between fentanyl administration and SSEP measurement may have allowed other factors to influence the results.

In summary, when isoflurane produced a sustained SSEP change that could be fit by an exponential, the time constant was essentially identical to the time constant of slow anesthetic uptake by the body, with anesthetic uptake described by a two-compartment model. At low isoflurane concentrations, SSEP changes were often small or not sustained, and the changes could not be fit by an exponential curve. Intravenous fentanyl was more likely to affect SSEP during low concentration isoflurane than high concentration. Although these data cannot be extrapolated directly to adult animals or humans, they suggest that the time-course of anesthetic effects on SSEP may be complex. Changes may be transient, and 30 or more minutes may be required for a change to reach a final value. The possibility of these types of complex SSEP changes should be considered both in studies of the effects of anesthetics on evoked potentials and during intraoperative monitoring of evoked potentials. Specifically, measures at multiple time points rather than single time points should be made after a change in anesthetic to avoid confusing transient with stable changes.

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1990;70:284–8

Enhancement of Fentanyl Analgesia by Clonidine Plus Verapamil in Rats

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HORVÁTH G, BENEDEK G, SZIKSZAY M. Enhancement of fentanyl analgesia by clonidine plus verapamil in rats. Anesth Analg 1990;70:284–8.

An investigation was made of the analgesic effects of the subcutaneous coadministration of fentanyl, an opioid μ-agonist (15 μg/kg), clonidine, an α_2-agonist (100 μg/kg), and verapamil, a calcium channel blocker (10 mg/kg) in rats. Nociceptive sensitivity was assessed with hot-plate and tail-flick techniques. None of the three drugs alone was associated with appreciable analgesic effects in the doses used. The simultaneous administration of the three drugs resulted in marked analgesia superior to that of all binary combinations of these drugs. Two-way analysis of variance showed statistically significant differences in hot-plate and tail-flick latencies after drug treatments ($P < 0.001$). The significant differences in the area under the time-response curve values ($P < 0.001$) might indicate not only an increased analgesic effect, but also a prolongation of antinociception. These results suggest the existence of hitherto unreported interactions between drugs involved in the production of analgesia.

Key Words: INTERACTIONS (DRUG)—fentanyl, clonidine, verapamil. ANALGESIA—fentanyl, clonidine, verapamil. ANALGESICS, FENTANYL. SYMPATHETIC NERVOUS SYSTEM, PHARMACOLOGY—clonidine. PHARMACOLOGY, VERAPAMIL.

Combinations of drugs are widely used to reduce the therapeutic doses of anesthetic agents as much as possible in an attempt to decrease side effects. Fentanyl, the most frequently used opioid in the anesthetic practice, is often a component of such combinations. The other adjuvants depend on the pharmacologic responses sought.

Clonidine is currently being advocated as a supplementary agent for anesthesia or analgesia (1–4). It is a centrally acting antihypertensive agent (5), which improves the perioperative hemodynamic and adrenergic stability and reduces fentanyl requirements (6,7). Clonidine exerts antinociceptive effects in several animal species (for a review, see 8) and in humans (9). Electrophysiologic (10) and behavioral (1) studies as well as clinical studies (6,11) have demonstrated potentiation of opiate analgesia by clonidine (12). The interaction appears to occur mainly at a spinal cord level (10,11), although there are reports of central mechanisms as well (8).

Calcium antagonists may also be used in clinical anesthesiology because of their potent vasodilatory action (13,14). Their use in the production of analgesia is new. Several groups have shown, however, that calcium antagonists may potentiate the analgesic effects of opiates in rodents (15–17). Recently, a combination of fentanyl and the calcium channel blocker nimodipine was successfully tried in humans during surgical anesthesia (18).

No attempt has been made to potentiate the analgesic effects of opiates with the combined use of calcium blockers and clonidine. We therefore designed an experimental study in rats to investigate the analgesic effects of the simultaneous administration of fentanyl, clonidine, and verapamil. Our data provide evidence of a major increase in the antinociceptive effect of fentanyl by clonidine and verapamil.

Materials and Methods

Male Wistar rats weighing 150–200 g were used. The animals were acclimatized to the laboratory environment for at least 2 wk before being used. They were kept under a regular light-dark schedule at an ambient temperature of 22° ± 1°C. Food and water were available continuously except during the experi-

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Table 1. Area Under the Time-Response Curve Values (mean ± SEM) in Hot-plate and Tail-flick Test After Drug Treatments

	Hot-plate test		Tail-flick test	
Treatment groups	*n*	$AUC_{(0-120\ min)}$ values	*n*	$AUC_{(0-120\ min)}$ values
Saline	5	552 ± 494	5	382 ± 170
VER (10 mg/kg)[a]	6	550 ± 441	6	344 ± 121
CLO (100 μg/kg)	18	2,210 ± 1,002	18	508 ± 94
FENT (15 μg/kg)	18	1,620 ± 514	23	458 ± 87
CLO + VER	11	3,845 ± 1,006	11	461 ± 174
FENT + CLO	6	2,720 ± 928	6	1,359 ± 98
FENT + VER	6	4,960 ± 1,138	18	780 ± 238
FENT + VER + CLO	10	11,910 ± 1,110	15	2,180 ± 297
F values		13.74[b]		14.26[b]
($df_{1,2}$)		(7,72)		(7,94)

AUC, area under the curve; CLO, clonidine; FENT, fentanyl; VER, verapamil.

[a] Doses are given in parentheses.

[b] Significant with one-way analysis of variance.

ments. All experiments were carried out at the same time of the day (9 AM–12 noon) to exclude diurnal variations in pharmacologic effects. Each rat was tested only once.

The nociceptive sensitivity was assessed using hot-plate (HP) and tail-flick (TF) techniques. Hot-plate and TF latencies were determined consecutively. The latency of licking one of the hind paws was measured on the HP (52°C, cut-off: 60 s). The TF technique was described by Janssen et al. (19) (53°C water; cut-off: 30 s). Drugs were injected subcutaneously (SC), and the altered nociceptive response was measured at 30, 60, and 120 min postinjection.

Drug solutions in the final concentrations were freshly prepared or diluted with physiologic saline and were injected simultaneously in a total volume of 2 mL/kg of body weight. The different groups were tested in random order, and the observer was unaware of the drug treatments. To search for a slightly effective analgetic dose of individual drugs, a dose-response curve was constructed for fentanyl (10–50 μg/kg SC) or clonidine (10–200 μg/kg SC). The experimental protocol for the combined administration of drugs is shown in Table 1.

The drugs included fentanyl—Fentanyl (Richter, Budapest); verapamil HCl—Verapamil (Orion, Helsinki), and clonidine HCl (Sigma).

The baseline response, measured before the administration of any drugs, was subtracted from the effect induced by the drugs. The area under the time-response curve ($AUC_{0-120\ min}$) was calculated for each rat. The data are expressed as mean areas ± SEM. The statistical significance of the drug treatments on analgesic response was assessed over time by two-way analysis of variance. The main effects tested were drug treatment (group) and time. Post hoc comparison was made with the Dunnett test at a significance level of 0.05.

The study was approved by the Animal Investigation Committee of Albert Szent-Györgyi Medical University.

Results

Dose-Response Effects of Individual Drugs

The analgesic efficacy of fentanyl (10, 15, 25, and 50 μg/kg SC) was tested in the two types of nociceptive test. Significant differences in HP latencies were observed by doses of fentanyl (F[3,66] = 5.88, $P < 0.001$), by time (F[2,66] = 9.11, $P < 0.001$), and for the interactions (F[6,66] = 3.12, $P < 0.01$). Significant differences in TF latencies were also observed by doses of fentanyl (F[3,99] = 35.84, $P < 0.001$), by time (F[2,99] = 21.28, $P < 0.001$), and for the interactions (F[6,99] = 5.94, $P < 0.001$).

The antinociceptive effect of clonidine (10, 50, 100, and 200 μg/kg SC) was tested using both nociceptive methods. Significant differences in latencies were observed by the doses of clonidine in both the HP test (F[3,78] = 3.58, $P < 0.05$) and the TF test (F[3,78] = 6.39, $P < 0.001$).

Coadministration of Drugs

Results of combined drug treatments were evaluated in eight experimental groups of rats (Table 1). The baseline latencies in the two nociceptive tests did not differ significantly between the groups (HP: 24.4 ± 3.14 s, F[7,72] = 0.97; TF: 3.07 ± 0.42 s, F[7,94] = 1.26).

The time-courses for the analgesic effects of representative fentanyl (15 μg/kg) and clonidine (100 μg/kg) doses in the presence or absence of verapamil (10 mg/kg) are shown in Figure 1, together with the effects of verapamil alone and those of physiologic saline on both nociceptive tests.

Although verapamil treatment alone failed to alter the latency values in both tests, simultaneous administration with a slightly effective dose of fentanyl resulted in an increased analgesic efficacy of fentanyl by time in both the HP (F[2,66] = 9.90, $P < 0.001$) and TF tests (F[2,81] = 12.23, $P < 0.001$).

Virtually identical results were obtained with a mixture of fentanyl (15 μg/kg) and clonidine (100 μg/kg) in both nociceptive tests. An injection of clonidine, which by itself had no discernible analgesic

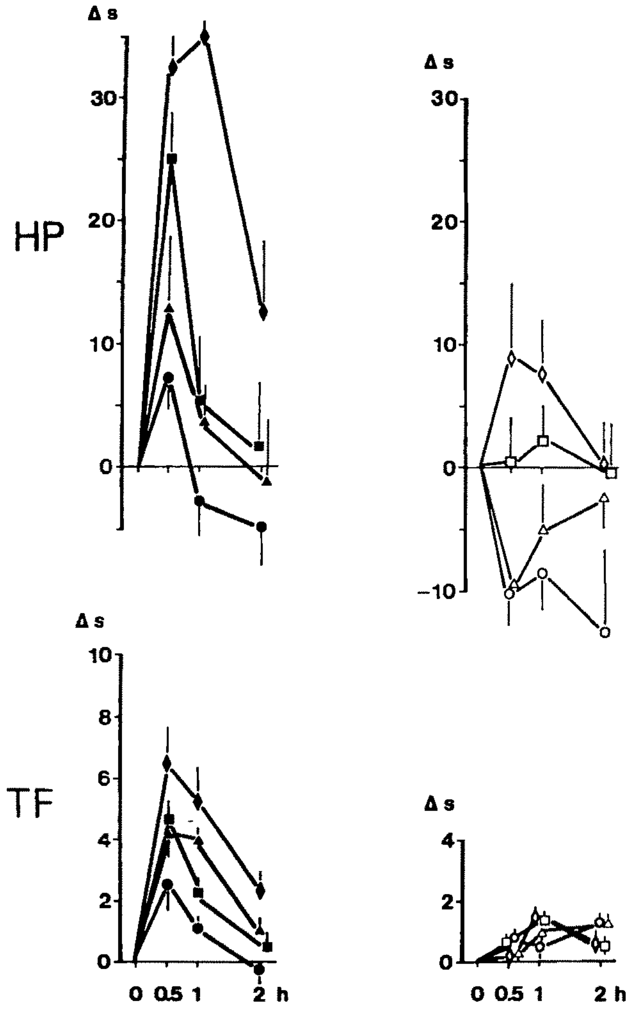

Figure 1. Time-course of the analgesic effects of the drugs in HP (*top*) and TF (*bottom*) tests in rats. Measurements were made before (0 time) and at three times after the SC injection of saline (△), 15 μg/kg fentanyl (●), 100 μg/kg clonidine (□), 10 mg/kg verapamil (○), fentanyl + verapamil (■), fentanyl + clonidine (▲), clonidine + verapamil (◇), and fentanyl + verapamil + clonidine (◆) at the doses indicated. Each point represents the mean changes in latencies after subtraction of basal values ± SEM.

effect, together with simultaneous administration of fentanyl resulted in a significant difference in the HP test from the fentanyl-alone group (F[2,66] = 6.14, *P* < 0.001). A similar increase in analgesic effect was observed in the TF test after this combined drug administration (F[1,81] = 17.17, *P* < 0.001).

The coadministration of the three drugs (clonidine, fentanyl, and verapamil) resulted in major increases in antinociception. The left side of Figure 1 shows the drastically increased analgesic effects of the mixture compared with the effects of fentanyl alone or the above binary combinations. Significant differences in HP latencies were observed by treatments (F[3,108] = 31.02, *P* < 0.001), by time (F[2,108] = 13.79, *P* < 0.001), and for the interactions (F[6,108] = 2.35, *P* < 0.05). Similar significant differences were obtained in the TF test by drug treatments (F[3,138] = 25.76, *P* < 0.001) and by time (F[2,138] = 20.24, *P* < 0.001). Prolongation of the analgesic effects was also observed after treatment with the mixture of the three drugs (Figure 1). The significant differences in area-under-the-curve values might indicate not only an increased analgesic efficacy, but also a prolongation of antinociception (F[3,36] = 27.43, *P* < 0.001).

Statistical analysis of the area-under-the-curve values also revealed an interesting feature in the comparison between groups (Table 2) in that clonidine-induced potentiation manifested itself mainly in the TF test, but verapamil-induced potentiation occurred mainly in the HP test.

Discussion

An important technique for decreasing side effects in pharmacology is the use of low doses of several agents that produce the same therapeutic effects. In our experiments, none of the three drugs was able, alone, to induce an appreciable analgesic effect in the dose used. The results show that the combination of all three drugs, i.e., the administration of fentanyl, an opioid μ-agonist, verapamil, a calcium channel blocker, and clonidine, a potent α_2-agonist, has a highly potentiated analgesic effect in rats. This combination was superior to all binary combinations in the HP test. It is noteworthy that no report has previously been published concerning the potentiating effect of verapamil on clonidine-induced analgesia.

On the other hand, the administration of a mixture of clonidine and fentanyl exerted a significant potentiation only in the TF test. Verapamil did not potentiate the analgesic effect of the clonidine plus fentanyl mixture in the TF test. Our results may provide additional evidence of the predominantly spinal site of action of clonidine in rats (12). Verapamil seems to be more effective in the HP test, which corroborates the supraspinal site of action of calcium antagonists (20).

It is difficult to interpret the potentiated analgesic effect of the combination of all three drugs. No previous data exist on the use of this combination for analgesia. It is tempting to speculate on the basis of calcium fluxes. Opiate effects have been attributed to a decreased synaptosomal calcium concentration (21). Calcium channel blockers impede the transmembranous calcium flow (22). Clonidine has similarly been reported to reduce the cortical synaptosomal calcium level in rats (23). We suggest, therefore, that the

Table 2. Significant t Values for Positive $AUC_{(0-120\ min)}$ Values Between Groups (See Text of Results)

Groups	Saline	FENT	CLO	VER	CLO + VER	CLO + FENT	FENT + VER	FENT + VER + CLO
Saline	—	NS	NS	NS	2.12 (15)[a]	NS	3.30 (10)	6.94 (14)
FENT	NS	—				NS	3.30 (23)	9.60 (27)
CLO	NS		—		NS	NS		6.16 (27)
VER	NS			—	2.31 (16)		3.61 (11)	7.02 (15)
CLO + VER	NS		NS	NS	—			4.96 (20)
CLO + FENT	4.97 (11)	5.00 (28)	4.87 (23)			—		5.69 (15)
FENT + VER	NS	NS		NS			—	4.11 (15)
FENT + VER + CLO	3.69 (20)	6.58 (37)	5.78 (32)	3.88 (21)	4.54 (25)	NS	2.81 (20)	—

CLO, clonidine; FENT, fentanyl; VER, verapamil.
On lower left side: tail-flick test; on upper right side: hot-plate test.
[a] Degrees of freedom indicated in parentheses.

interaction of calcium channel blockers and α_2-agonists on the analgesic effects of opiates takes place at the level of transmembranous calcium currents. It is interesting, however, that the effects of α_2-adrenoceptor agonists on the smooth muscle require a calcium influx, and therefore calcium antagonists can reduce postsynaptic α_2-adrenergic vascular effects (24,25). α_2-Agonists hyperpolarize the cell membranes in the locus coeruleus (26), whereas they hypopolarize smooth-muscle cells (24). This might be connected with the differences between the vascular and analgesic effects of clonidine. The fact that calcium channel antagonists potentiate the anesthetic effect of nitrous oxide, which is not metabolized at all, seems to contradict a pharmacokinetic explanation of the phenomenon of potentiation (27). Therefore, we can suggest that calcium may be involved in the actions of analgetics. There are additional favorable aspects of the mixture of the three drugs we studied. A beneficial feature of the interaction between calcium blockers and opiates is that whereas the analgesic effect seems to be facilitated, the respiratory depressant effect of opiates is reduced by verapamil (28). Finally, it is worth mentioning that both clonidine and calcium channel blockers have frequently been used as adjuvant drugs during surgery.

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Hyperbaric Nitrous Oxide as a Sole Anesthetic Agent in Humans

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RUSSELL GB, SNIDER MT, RICHARD RB, LOOMIS JL. Hyperbaric nitrous oxide as a sole anesthetic agent in humans. Anesth Analg 1990;70:289–95.

Nitrous oxide (N_2O) has been used to produce analgesia and anesthesia for more than 100 yr. However, because of its high MAC value (1.04), general anesthesia with N_2O can usually be attained only in a hyperbaric environment. Because of the sparsity of documentation for human physiologic responses to hyperbaric N_2O, we studied eight male volunteers at 2 ATA (1520 mm Hg) anesthetized with N_2O only for periods of 2–4 h. N_2O partial pressures ranged from 836 to 1368 mm Hg. The anesthetic state was associated with tachypnea, tachycardia, increases in systemic blood pressure, mydriasis, diaphoresis, and at times, clonus and opisthotonus. A stable level of physiologic activity was difficult to maintain.

Key Words: ANESTHETICS, GASES—nitrous oxide. HYPERBARIA, NITROUS OXIDE.

Nitrous oxide (N_2O) is the most widely used inhalation anesthetic agent in humans. The inhaled concentration required to produce general anesthesia (the minimum alveolar concentration, or MAC, is 104% or 1.04 atmospheres absolute [ATA]) dictates that it must be used as an adjunctive anesthetic agent in most people (1). It can be used as the sole agent for general anesthesia only in hyperbaric conditions under which the MAC value can be reached or exceeded with a nitrous oxide/oxygen (N_2O/O_2) mixture that will not result in hypoxemia. Despite Paul Bert's early demonstration of general anesthesia with hyperbaric N_2O and later use for surgical anesthesia, its anesthetic value and physiologic effects at increased atmospheric pressures have not been clearly defined (2,3). Studies by various investigators have evaluated small groups of human volunteers or animal subjects to determine the capability of N_2O general anesthesia administration without subject hypoxemia (4), to evaluate the physiologic changes with attempted induction of anesthesia (5), to study its psychological and electroencephalographic effects in subanesthetic doses (6), to determine MAC values (7), and to determine its effects on ventilation (8,9). In many of these studies N_2O was administered at normobaric pressure, effects were followed for only short time periods, or the specific effects studied were quite limited. When N_2O was administered at increased atmospheric pressure, hyperbaric pressures were varied or subanesthetic concentrations of N_2O were administered. Although anesthetic concepts for N_2O (such as MAC) have been delineated, questions remain regarding many aspects of its use: the time-course of induction and emergence; the ability of spontaneously breathing anesthetized subjects to maintain normocapnea during N_2O anesthesia; the presence or absence of seizure activity; maintenance of adequate continuous arterial oxygen (O_2) saturation during prolonged general anesthesia; physiologic changes as the duration of anesthesia is prolonged; and the true breath-by-breath end-tidal N_2O levels (as measured by mass spectrometry) necessary to maintain anesthetic stability. We recently used N_2O as the sole anesthetic agent in healthy human volunteers during a study of methionine synthase inactivation. Here we report the physiologic effects of induction and maintenance of N_2O general anesthesia under stable hyperbaric conditions.

Methods

After approval by the institutional Clinical Investigations Committee, eight ASA physical status I male

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volunteers, ages ranging from 20 to 31 yr, were recruited. Each anesthetic was performed in a hyperbaric chamber that was 2.75 by 3.66 m with a 2.44-m-high ceiling (9 × 12 × 8 ft). The chamber itself was initially ventilated with air at 1750 L/min; this was later increased to 3500 L/min. The chamber was stocked with all emergency drugs and routine anesthetic equipment.

Conduct of Anesthesia

All subjects were monitored by electrocardiogram, automatic blood pressure measurement by oscillometry, blood pressure by aneroid sphygnomanometer, ear oximetry, a precordial stethoscope, and an axillary temperature probe. A mass spectrometer mounted outside the chamber was used for breath-by-breath analysis of end-tidal N_2O, carbon dioxide (CO_2), and O_2. A Neurotrac or Nomad compressed spectral array monitored cerebral electrical activity during anesthesia.

Before administration of anesthesia all subjects fasted for more than 8 h. An 18-gauge intravenous catheter was inserted into a forearm vein and lactated Ringer's solution was administered as the maintenance intravenous fluid. During each anesthetic, two anesthesiologists and one nurse were present within the chamber. The chamber was pressurized to 1520 mm Hg or 2 ATA with compressed air. During the anesthetic period, attending personnel inside the chamber breathed ambient air with an O_2 partial pressure of 319 mm Hg. Exhaled gases from the expiratory limb of the breathing circuit were scavenged through a variable resistance tubing and exhausted to outside the chamber by the chamber-ambient pressure difference through a conduit in the chamber wall.

Each subject initially breathed spontaneously by facemask. Unconsciousness was induced by vital capacity breaths of N_2O/O_2 (1140 mm Hg N_2O:380 mm Hg O_2) from a Heidbrink Kinet-o-meter anesthesia machine. After stabilization of blood pressure, pulse rate, and respiratory pattern, succinylcholine was given (20 mg followed by 1.5 mg/kg) followed by tracheal intubation. Ventilation was assisted manually with a 3-L bag on the anesthesia machine until resumption of adequate spontaneous respirations. An 18-F orogastric tube was placed to allow gastric decompression. Anesthesia was maintained with N_2O/O_2 for 4 h in six subjects, 3 h in one subject, and 2 h in one subject. Anesthesia was adjusted so that each subject would breathe spontaneously and quietly through the endotracheal tube. Otoscopic examinations were repeatedly performed during the anesthetic. At the end of anesthesia, awakening occurred while chamber pressure was maintained at 1520 mm Hg. Washout of N_2O was monitored during spontaneous breathing of high flow 100% (1520 mm Hg) O_2. After awakening and stabilization, chamber pressure was gradually decreased. An empiric decompression stop of 30 min was taken at 990 mm Hg, a pressure equivalent to a depth of 3.05 m (10 ft) of salt water.

Mass Spectrometry of Respiratory Gases

A Perkin-Elmer MGA 1100 mass spectrometer was positioned outside the hyperbaric chamber. A capillary tube joined each subject's endotracheal tube connector to the mass spectrometer after passing through a conduit in the chamber wall. A pressure divider system outside the chamber enabled the mass spectrometer to measure breath-by-breath end-tidal N_2O, CO_2, and O_2 both at a stable hyperbaric pressure and during increasing or decreasing chamber pressures. This allowed fine adjustments in measured anesthetic levels to be made and ventilatory adequacy and O_2 delivery to be rapidly determined (10).

Atmospheric gas samples from inside the chamber were collected in airtight glass syringes during the anesthetic for trace N_2O analysis. The N_2O levels were later measured by a Hewlett Packard 5890A gas chromatograph/mass spectrometer. The N_2O exposure of the attending personnel and thus the adequacy of the chamber ventilatory system was determined.

Changes in hemodynamic measurements were compared using Student's *t*-test. A *P* value of ≤ 0.05 was considered significant.

Results

Nitrous Oxide General Anesthesia

General anesthesia (unconsciousness, analgesia, and amnesia) was maintained in all subjects for up to 4 h with careful titration of the inhaled N_2O partial pressure based on clinical assessment of the subject and oxygen saturation by ear oximetry and the end-tidal N_2O and CO_2 values. General anesthesia was maintained with the end-tidal N_2O ranging between 836 and 1368 mm Hg (1.1–1.8 ATA).

Induction of anesthesia by one to three breaths of 1.5 ATA (1140 mm Hg) of N_2O was characterized by tachypnea, tachycardia, and hypertension. Consciousness was lost in less than 60 s. There was a rapid transition through stage 2 (Guedel) to the third plane of stage 3 with rapid, regular small tidal volume respirations. During induction mean arterial blood pressure increased by a mean of 38 mm Hg. Systolic blood pressure increased to 171 ± 17 from 124 ± 9 mm Hg and diastolic to 102 ± 9 from 67 ± 9 mm Hg ($P < 0.001$). Heart rates also increased to 91 ± 21 from a preinduction mean of 57 ± 12 beats/min ($P = 0.002$). Respiratory rates ranged between 10 and 20 breaths/min during induction. Peak increases in heart rate, blood pressure, and respiratory rate were attained before administration of succinylcholine and intubation. Intubation did not result in significant hemodynamic changes.

During both the induction and initial stabilization periods, α- and β-wave activity, as recorded on the compressed spectral array, decreased, with generalized slow-wave activity becoming dominant. Electroencephalograph wave amplitudes increased.

During maintenance of anesthesia, all subjects continued to have rapid shallow respirations ranging from 20 to 40 breaths/min. One subject developed prolonged tachypnea of 54 breaths/min. Tachypnea was consistently present except at high end-tidal N_2O levels (about 1.7–1.8 ATA). At this level, respirations slowed and respiratory sensitivity to hypercapnea decreased. Two subjects became apneic, necessitating manually assisted ventilation. Oxygen saturation, by ear oximetry, was maintained at above 95%. As the duration of general anesthesia lengthened, heart rate and blood pressure decreased toward preinduction levels. However, interspersed with this trend were short periods of increased autonomic activity characterized by increases in heart rate and blood pressure, mydriasis, and marked diaphoresis. There were no significant disturbances of cardiac rhythm.

Most subjects exhibited periods of marked abdominal muscle rigidity, often followed by signs of increased sympathetic discharge and catatonic limb movement. This was often associated with eye opening, but nonresponsiveness to verbal commands and pain (sternal rubbing) continued. With these changes, the compressed spectral array also exhibited periods of increased α and β fast-wave activity, predominantly in the subject's dominant cerebral hemisphere. Short periods of muscular activity alternated with longer periods of relaxation. All subjects developed periods of dysconjugate gaze, and clonus could be demonstrated in both upper and lower extremities. Four subjects had opisthotomic posturing that subsided and cleared in response to an increase in the inhaled N_2O concentration. At no time was there evidence of seizure activity on the compressed spectral array.

Awakening was characterized by a short but prominent stage 2 with increased patient movement, tachypnea, continued unawareness, and postanesthetic amnesia. High O_2 flow rates (>10 L/min) speeded N_2O washout and shortened this period. All subjects followed verbal commands within 15 min.

One of the eight subjects had severe nausea and vomiting in the postanesthesia period, whereas four had mild to moderate gastrointestinal upset. No subjects experienced decompression sickness. Tympanic membrane examinations were normal during and after anesthesia.

General anesthesia with hyperbaric N_2O is associated with hypertension, tachycardia, tachypnea, bursts of increased sympathetic nervous system activity, and at times clonus and opisthotonus. No prolonged residual effects were noted.

Respiratory Gas Analysis

End-tidal respiratory gas analysis allowed adjustment of inspired O_2 concentration and anesthetic gas levels, as well as respiratory rate and volume, in order to treat the hypercapnea associated with apnea. During anesthesia the inspired O_2 concentration varied from 0.2 ATA (152 mm Hg) to 1.8 ATA (1366 mm Hg) and up to 2.0 ATA (1520 mm Hg) during awakening. Normocapnea was assured by monitoring of end-tidal CO_2, which ranged from 3.6% to 4.6%, except during apnea induced by 1.8 ATA (1378 mm Hg) N_2O. Decreased inspired N_2O and assisted ventilation quickly resulted in resumption of adequate spontaneous ventilation.

At the initial chamber ventilation rate of 1750 L/min, samples of chamber air had more than 2500 parts per million (ppm) of N_2O. When chamber ventilation was increased to 3500 L/min, N_2O levels decreased to 25–75 ppm. Subjectively, the attendants inside the chamber experienced no untoward effects.

Discussion

General anesthesia with N_2O for surgical procedures was initially reported in 1848 (11). Although its physiologic effects have been extensively studied, most information comes from studies of subject exposures at normal atmospheric pressures, during which N_2O had been used as one of a combination of anesthetic agents, or during short hyperbaric exposures without use of modern monitoring techniques and equipment. We have studied the effects of hyperbaric N_2O used as a sole anesthetic agent for as long as 4 h in human volunteers. This is the first study to use mass spectrometry for measurement of anesthetic and respiratory gas concentrations, to monitor electroencephalographic activity by compressed spectral array analysis, and to evaluate pollution of the hyperbaric chamber by N_2O during general anesthesia of human volunteers.

Hyperbaric Nitrous Oxide Anesthesia in the Past

Nitrous oxide was used as a general anesthetic agent in France during the mid 1800s before the time of Paul Bert. Bert, however, was the first to administer hyperbaric N_2O to humans (3). It was administered at 1.2 ATA (920 mm Hg) to 14 patients breathing a mixture of 15% (138 mm Hg) O_2 and 85% (782 mm Hg) N_2O for procedures as diverse as mastectomies, suborbital nerve resection, and repair of shoulder dislocations. The total anesthetic times ranged from 4 to 26 min. Unconsciousness and muscle relaxation were said to be obtained, although one patient was described as talking throughout the procedure despite chamber pressure being increased to 1020 mm Hg. Patient monitoring consisted of only attendant observation.

There have been other experimental exposures of humans to hyperbaric N_2O, but exposures have either been very short or monitoring has been limited. Faulconer and Pender monitored five subjects with a two-channel electroencephalograph and a compensating Millikan oximeter during short, 3.5–15-min exposures to 760 mm Hg N_2O at 2 ATA (4). In two volunteers, Smith et al. studied the induction time (or "the time to no response") of N_2O at pressures from 1 to 2 ATA (5). Monitoring included electrocardiogram, systolic blood pressure, pulmonary ventilation, bifrontal electroencephalogram, and end-expired N_2O (by a Grubb Parsons MEDI infrared gas analyzer). However, these exposures were for a maximum of only 3 min. When Hornbein et al. anesthetized seven volunteers with hyperbaric N_2O for MAC determination, each subject was monitored hemodynamically with both an arterial and a central venous catheter (7). They also measured the inspired partial pressure of O_2 at 1 ATA with either an IBC polarographic electrode or a Beckman E2 O_2 analyzer. The duration of anesthesia ranged from 2.5 to 3 h. Modern monitoring and a longer duration of anesthesia have allowed us to evaluate the physiologic effects of hyperbaric N_2O more thoroughly than in the past.

Uptake and Distribution

In the present study, general anesthesia was induced in all eight volunteers in less than 60 s by one to three breaths of 1.5 ATA (1140 mm Hg) N_2O. Being odorless and nonpungent, the N_2O/O_2 was easily and smoothly inhaled. The low blood-gas solubility coefficient of N_2O (0.47) allowed a maximal alveolar partial pressure to be quickly obtained at induction and maintained for the duration of anesthesia. Subjects passed rapidly through the excitement phase (stage 2) to deeper levels of anesthesia.

Rapid induction of general anesthesia is in keeping with reports from previous studies. During Paul Bert's original human anesthetics with hyperbaric N_2O, unconsciousness was said to be obtained within 15 s to 2 min (2). Faulconer and Pender reported loss of consciousness in each of their five subjects in less than 2 min during administration of 50% N_2O in O_2 at 2 ATA (4). Smith et al. induced anesthesia in two subjects with concentrations of 100% N_2O and 92%, 87%, or 80% N_2O with O_2 at 1 ATA as well as 50% N_2O with O_2 at 2 ATA and 85% N_2O with O_2 at 1.2, 1.4, 1.6, and 2 ATA (912–1520 mm Hg) (5). The induction times were shorter during inhalation of the higher N_2O partial pressures, ranging from 45 s with 1240 mm Hg to 105 s with 760 mm Hg of N_2O. It was noted that each subject's time to no response was shorter for hypoxic, as compared to normoxic, gas mixtures, despite the same N_2O partial pressure.

Previous studies did not measure breath-by-breath levels of end-tidal N_2O by mass spectrometry during induction, maintenance, and emergence from anesthesia. Smith et al. did use an infrared gas analyzer during their short hyperbaric exposures (5). Hornbein et al. calculated the partial pressure of N_2O breathed at 1 ATA (7). Changes in inspired N_2O partial pressure were effected by changing chamber pressure, necessitating a recalculation with each chamber pressure alteration. The ability to continuously monitor end-tidal gas concentrations at 2 ATA allowed us to determine that 1140 mm Hg of N_2O resulted in both rapid loss of consciousness and rapid washout of residual pulmonary nitrogen.

After 4 h of hyperbaric N_2O anesthesia, high flows of inspired O_2 (10 L/min) quickly washed out residual N_2O with rapid return of consciousness. In the present study, after 4 h of general anesthesia, all subjects followed commands and performed simple mathematical computations within 15 min of discontinuation of N_2O. Paul Bert's patients recovered consciousness within approximately 1 min (2). Faulconer and Pender reported return of consciousness in less than 2.5 min (4), whereas Smith et al. reported that one subject appeared inebriated for 45 min, despite the fact that he had breathed N_2O (1034 mm Hg) for less than 3 min (5). Although Hornbein et al. subjected their volunteers to partial pressures of N_2O

and exposure durations similar to those that we report, they did not comment on emergence (7).

Central Nervous System Effects

The subjects and investigators in the present study benefitted from the availability of modern monitoring equipment. Perhaps one of the most vital aspects of this included careful evaluation of the central nervous system throughout the anesthetic. Recording of the compressed spectral array was begun before induction and continued for the duration of anesthesia. Induction of anesthesia was associated with a rapid decrease in both α- and β-activity that continued throughout the anesthetic period, except for periodic bursts of both α- and β-waves over the subjects' dominant hemispheres, which appeared and disappeared at irregular intervals. Faulconer and Pender, using a two-channel electroencephalograph in four of five subjects breathing 760 mm Hg of N_2O, found that α-wave activity decreased during induction of anesthesia at stage 1 and disappeared during stage 2, with predominately δ-wave activity continuing (4). In one of their subjects, α-wave activity did not decrease. Smith et al. also reported that increased depth of anesthesia from hyperbaric N_2O and the associated lack of response to stimulation was associated with a preponderance of higher amplitude, slow wave cortical electrical activity (5).

Electrical seizure activity was not demonstrated at any time in any of the subjects studied by either previous investigators or ourselves. However, convulsions have been well documented in mice after N_2O breathing has been terminated (12,13). Conversely, N_2O has also been shown to be a potent anticonvulsant in cats during enflurane anesthesia (14).

Neurological signs other than seizures often develop during anesthesia with hyperbaric N_2O. Both clonus and opisthotonic posture (the latter less frequently) have been previously reported during hyperbaric N_2O anesthesia (7). Opisthotonic posturing has also been observed in mice during general anesthesia with isoflurane, enflurane, or halothane (15). With these volatile anesthetics, opisthotonus was ascribed to inhibition of the facilitating cells of the reticular formation. This differential rate of depression within the central nervous system stimulated sensitive stretch reflexes and resulted in opisthotonus. In the present study, increasing the inspired partial pressure of N_2O caused opisthotonus, muscle rigidity, and jerky limb movements to subside. This raises the possibility that opisthotonus is actually associated with a prolonged excitement phase of the anesthetic state. In contrast to our findings, Hornbein et al. reported that muscle rigidity and jerky limb movements subsided after the partial pressure of inhaled N_2O was decreased from 1188 to 836 mm Hg (1.5 to 1.1 ATA) (7).

Increased activity of the sympathetic nervous system has been previously observed during hyperbaric N_2O exposure (7). In the present study these "bursts" of sympathetic activity included mydriasis and marked diaphoresis and were associated with hyperdynamic circulatory responses. Episodes occurred at end-tidal N_2O partial pressures ranging from 1.1 to 1.7 ATA (836–1292 mm Hg) and varied widely between individuals. In cats, the increased sympathetic activity resulting from N_2O exposure can be suppressed by resection of the brainstem at the midcollicular level (16). This suggests that the increased sympathetic activity in cats was mediated at the suprapontine level. Such observations may be applicable to humans.

Cardiovascular Effects

The increased sympathetic nervous system activity associated with hyperbaric N_2O resulted in marked stimulation of the cardiovascular system. Induction of anesthesia by vital capacity breaths of hyperbaric N_2O resulted in both tachycardia and hypertension. In the present study heart rate increased by a mean of 31 beats/min and mean arterial blood pressure increased by 38 mm Hg. Smith et al. reported a varied response in two subjects and believed that anxiety may have been a major factor causing tachycardia and hypertension in the one subject who exhibited these responses (5). We also observed hyperdynamic cardiovascular responses during the "bursts" of sympathetic nervous system activity with pulse and blood pressure increasing, although not to the same extent as during induction. In dogs, although 760 mm Hg of N_2O has been shown to decrease myocardial contractility and myocardial stroke work, this general depression of function can have periods of cardiac stimulation similar to the sympathetic "bursts" demonstrated by our human volunteers interspersed (17,18). In the canine model, these periods of stimulation are associated with mydriasis, increased arterial and right atrial blood pressures, increased systemic vascular resistance, and increased norepinephrine levels in the pulmonary circulation (19,20). In humans the increases in blood pressure and pulse rate occur at the same time as increased α- and β-wave activity on the compressed spectral array. As the duration of anesthesia increased there was also a gradual trend for both pulse rate and blood pressure to decrease toward preinduction levels.

Respiratory Effects

The respiratory system is also stimulated during hyperbaric N_2O anesthesia. Tachypnea quickly developed in all our subjects after induction of anesthesia. Although respiratory rates were 10–20 breaths/min during induction, rates ranged from 13 to 57 breaths/min but were usually maintained between 20 and 40 breaths/min during maintenance of anesthesia for 4 h. Normal end-tidal CO_2 levels could be maintained with spontaneous ventilation, but at end-tidal N_2O partial pressures above 1216 mm Hg (1.6 ATA) we noted a decrease in the subjects' ventilatory response to hypercarbia. This was associated with the onset of apnea at 1368 mm Hg (1.8 ATA) of N_2O and required manually assisted ventilation. The ability of N_2O to decrease the usual respiratory response to increases in CO_2 in human and animal models has been demonstrated to occur both with normal and with artificially increased resistance to breathing (8,9,21). This effect may be secondary to selective depression of peripheral chemoreceptor function. Spontaneous ventilation resumed in our subjects after the partial pressure of inhaled N_2O was reduced. Similar effects were not noted in previous studies, as end-tidal CO_2 was not monitored; in the one study in which expired N_2O was measured hyperbaric N_2O exposure was for less than 3 min.

Gastrointestinal Effects

The sympathetic stimulation may have also affected the gastrointestinal system. Nausea and vomiting have been reported as a significant problem in patients anesthetized with hyperbaric N_2O (7). During routine surgical anesthesia, N_2O is believed to be a contributing factor to postoperative nausea and vomiting as well (22,23). Nausea and vomiting may also be related to increased middle air pressure secondary to N_2O accumulation, stimulation of opioid receptors, and/or gastric distention (24). Of the eight subjects anesthetized with hyperbaric N_2O in this study, one developed marked nausea and vomiting and four had milder gastrointestinal upsets. Otoscopic examination both during anesthesia and in the immediate postoperative period revealed normal tympanic membranes and no change from the baseline examination before induction.

Value of MAC

Nitrous oxide may be associated with nausea and vomiting, but it also produces analgesia and anesthesia. The MAC value of N_2O in humans is reported by Hornbein et al. to be 1.04 ATA (790 mm Hg) (7). After determining the MAC of human volunteers as assessed by a tetanic electrical stimulus (a 100-Hz pulse of 0.1-ms duration at 80–110 V) during general anesthesia with hyperbaric N_2O, these investigators believed that true MAC may have been underestimated: the true alveolar partial pressures of N_2O in their studies may have been higher than calculated as inhaled and end-tidal N_2O levels were not directly measured. The electrical stimulus may also have been inadequate. Although we did not specifically test for MAC in anesthetized subjects, it was noted that a partial pressure of N_2O greater than 1.2 ATA (912 mm Hg) was required for subjects to rest quietly during laryngeal and tracheal suctioning. Laryngeal suctioning provides a stimulus quite different than either electrical stimulation or surgical incision of the skin, so this does not necessarily mean that MAC is greater than 1.04 ATA. When MAC values for N_2O are extrapolated during studies of the additive effects of anesthetic agents, the MAC of N_2O in rats has been estimated to be from 1.36 ATA to 2.2 ATA (25,26). The MAC value for N_2O may require reconsideration.

Chamber Air Contamination and Nitrogen Narcosis

Administering volatile anesthetic agents under hyperbaric conditions must also be considered from the view of potential effects on the anesthesiologist. Both chamber contamination with the anesthetic gas or gases and the possible influences of breathing compressed air with an increased nitrogen partial pressure can affect both mental and manual performance. There was significant chamber air contamination with N_2O (up to 2500 ppm), which was greatly decreased by doubling chamber ventilation up to 3500 L/min. Maximal contamination occurred during induction of anesthesia by spontaneous breathing of 1.5 ATA N_2O by facemask. Scavenging of exhaled gases through the chamber wall via a conduit with an adjustable rate of gas evacuation was used to attempt to limit chamber spillage. Chamber contamination with anesthetic gases at hyperbaric pressures can be an important factor to consider so that attending personnel function is not compromised.

Nitrogen itself can induce a significant narcosis (27). However, this is usually at pressures greater than 100 ft of seawater or 4 ATA (3040 mm Hg) in scuba or chamber divers. Stupor, confusion, and depression of function can develop. There is some variation in individual susceptibility as well as possible interactions with sedating drugs at such depths. At 2 ATA performance of mathematical calculations becomes more difficult. When administering anesthesia in a hyperbaric chamber, it is important to consider the effects on the anesthesiologist as well as the subject.

Hyperbaria itself is not a factor causing the physiologic changes occurring during anesthesia with hyperbaric N_2O. No significant hemodynamic, respiratory, or central nervous system effects have been noted at pressures of 1520 mm Hg (12).

Conclusion

Although N_2O has been used as an analgesic and an adjunctive general anesthetic agent for well over 100 yr, there has been very limited experience in its use as a sole anesthetic agent under hyperbaric conditions. Much of its early use as an anesthetic agent at 1.2 ATA may have been associated with hypoxemia, and its presumed anesthetic effects may have been caused in part by this lack of O_2 in subjects. When administered under more controlled conditions, where hypoxemia is eliminated, its use is associated with hypertension, tachycardia, and tachypnea. Bursts of sympathetic nervous system activity result in mydriasis and sweating. Release of cerebral inhibitory influences results in muscle rigidity, clonus, and opisthotonus without evidence of seizure activity. Careful measurement of inhaled and end-tidal N_2O has demonstrated both rapid induction of and emergence from anesthesia but has raised questions as to the true MAC value of N_2O. Although it causes tachypnea, a partial pressure of 1216 mm Hg N_2O causes respiratory depression. As the sole anesthetic agent, N_2O is less than ideal. Its use as an adjunctive agent is in better keeping with desired effects on the anesthetized patient.

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Continuous In Vivo Measurement of Hepatic Lipoperoxidation Using Chemiluminescence: Halothane and Chloroform Compared

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COHEN PJ, CHANCE B. Continuous in vivo measurement of hepatic lipoperoxidation using chemiluminescence: halothane and chloroform compared. Anesth Analg 1990;70:296–8.

Hepatic necrosis, rarely occurring after administration of modern halogenated general anesthetics, has been ascribed to free radical-induced lipoperoxidation. As evaluation of hepatic chemiluminescence has been shown to provide a noninvasive assay for oxidative radical reactions, we have made continuous in vivo measurements of hepatic light output in the phenobarbital-induced halothane anesthetized rat and compared them with observations made during chloroform anesthesia. Chloroform produced a far more rapid and more profound increase in chemiluminescence, a phenomenon probably related to depletion of hepatic glutathione. These findings are consistent with significant differences in hepatic pathology associated with the two agents.

Key Words: ANESTHETICS, VOLATILE—halothane, chloroform. LIVER, TOXICITY—halothane, chloroform. TOXICITY, HEPATIC—halothane, chloroform.

Hepatic necrosis as a consequence of uneventful general anesthesia is a rare but potentially lethal event. It has been suggested that lipoperoxidation of hepatic cell membranes by active free radicals produced during metabolism of the anesthetic may be responsible for this phenomenon (1). That oxygen-derived free radicals might play a causative role in pathology as disparate as reperfusion injury after ischemia of the heart, intestine and brain, rheumatoid arthritis, and immune injury to lung and kidney has been suggested in recent reviews (2,3). The ability to detect free radical-induced lipoperoxidation in vivo would be of considerable value both in evaluating a drug's potential for inducing this toxicity and in developing therapies for treatment and prevention.

Spontaneous emission of extremely low-intensity light (chemiluminescence) by organs not possessing a luciferin/luciferase system was described in 1961 (4). It has been proposed that changes in organ chemiluminescence might be used as a continuous nondestructive assay of lipoperoxidation resulting from oxidation or reduction by one of several species of oxygen free radicals (5,6). The biochemistry of low-level chemiluminescence has been the subject of a recent review (7).

Brown (8) used an in vitro assay technique to demonstrate that hepatotoxicity of chloroform (trichloromethane) in the phenobarbital-induced rat is associated with hepatic microsomal lipoperoxidation. This process was accompanied by both increased concentrations of diene conjugates and a marked decrease in glutathione stores. Our continuous in vivo measurements of hepatic chemiluminescence in similarly treated animals paralleled these findings (9). In the same study, inhalation of isoflurane (1-chloro-2,2,2-trifluoroethyl difluoromethyl ether), an anesthetic subject to minimal biodegradation, was not associated with increased chemiluminescence.

In vitro measurements have shown the effect of halothane (2-bromo-2-chloro-1,1,1-trifluoroethane) on hepatic lipoperoxidation to be quantitatively different from that of chloroform: diene conjugates increased to the same extent as in chloroform-treated animals, but glutathione stores remained intact after administration of halothane. Significant differences in histologic changes were not unexpected in view of these two patterns of chemical alterations: livers from the animals anesthetized with chloroform showed marked centrilobular necrosis, whereas halothane anesthesia produced only minor pathologic changes (10).

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In vitro measurements performed after killing the anesthetized animal provide only a single observation in each subject, whereas observation of chemiluminescence can offer a continuous in vivo assay. Accordingly, the following study was performed to answer two questions: (a) Are there quantitative differences in the pattern of hepatic light emission when halothane and chloroform are compared? (b) If so, might this explain the significant differences in the histologic and biochemical alterations produced by the two anesthetics?

Methods

This investigation was approved by our institutional Animal Care and Use Committee. Hepatic chemiluminescence was evaluated in six male phenobarbital-induced Wistar rats weighing 180–200 g. Microsomal induction was accomplished by adding phenobarbital (1 mg/mL) to the drinking water for 5 days preceding each study. Chemiluminescence of the liver, exposed by a small laparotomy, was measured continuously using a photomultiplier (EMI 9653) cooled to −23°C, an amplifier-discriminator (model 1121, Princeton Applied Research), a frequency counter (Heathkit 1B 1100), and a recorder (5). After anesthesia was induced with intraperitoneal pentobarbital (75 mg/kg), a 30-min period of inhalation of air verified stability of the preparation. After this, administration of 1.3% halothane in air was begun and continued for 2 h while hepatic chemiluminescence was continuously observed; the animals were then killed. In this investigation, observations were not made upon discontinuation of the anesthetics. These data were compared with measurements that had been made in six animals in a previous investigation examining the effects of chloroform anesthesia (9). Because of the possibility of introducing error by comparing the present data (halothane) with the previously performed studies (chloroform), an additional four animals were evaluated contemporaneously: two were exposed to halothane and two received chloroform. Finally, two animals anesthetized only with pentobarbital were studied for a 150-min period to determine the effect of time on the measurements. The 18 animals involved in the study were all treated identically. Statistical analyses were facilitated with paired and unpaired Student's *t*-tests.

Results

No changes in chemiluminescence were observed during the 150-min observation period in the two control animals.

Table 1. Effect of Chloroform and Halothane on Rat Liver Chemiluminescence

	Chloroform		Halothane	
	Time (min)	Counts/s	Time (min)	Counts/s
Control	0	825 ± 69	0	897 ± 44
Onset	15.6 ± 1.6	N/A	30.0 ± 2.1	N/A
Peak	26.9 ± 2.5	1889 ± 102	63.0 ± 3.2	1221 ± 94

Mean ± SEM ($n = 8$ for each anesthetic). Both agents produced significant increases in chemiluminescence; however, with chloroform the magnitude of change ($P < 0.001$) was considerably greater and the time to onset ($P < 0.001$) much less. Chloroform and halothane differ significantly: time to onset of increased chemiluminescence, $P < 0.001$; time to maximum increase in chemiluminescence, $P < 0.001$; magnitude of maximum increase in chemiluminescence, $P < 0.001$. Chemiluminescence is increased significantly by chloroform, $P < 0.001$; halothane, $P < 0.01$.

Comparison of the effects of halothane and chloroform on hepatic chemiluminescence in the phenobarbital-induced rat is shown in Table 1. Data in the two recently studied animals receiving chloroform did not differ from their historical cohorts; similarly, the last two rats receiving halothane produced data similar to the initial six. Final data therefore are derived from eight animals in each of the anesthetized groups. Hepatic light output was identical in the control periods that preceded administration of either chloroform or halothane ($P > 0.5$); during these 30 min, hepatic light output remained constant. Chemiluminescence began to increase 30 min after administration of halothane, twice as long as that after an equipotent dose of chloroform ($P < 0.001$).

There was a significant increase ($P < 0.01$) in chemiluminescence accompanying halothane. However, peak levels were not attained until more than 1 h after administration of halothane, more than twice that observed with chloroform ($P < 0.001$). The increase in light emission accompanying halothane was only one-third that which had been observed with exposure to chloroform ($P < 0.001$). In both groups of anesthetized animals, light emission remained constant during the remaining periods of observation.

Discussion

The utility of measuring chemiluminescence in investigation of free radical-induced lipoperoxidation has been suggested by a number of studies. Low-level chemiluminescence occurs as a result of the generation of electronically excited states; when these excited species decay, light emission is produced (11). Light emission may result from decay of singlet oxygen generated by reaction of peroxy radicals, as well as by formation of 1,2-dioxetane derivatives (5). Chemiluminescence accompanying lipoperoxidation has been shown to occur during infusion of hydroperoxide into liver, brain, and lung as well as during hyperbaric oxygenation of liver and brain (7). Similarly, exposure of cardiac submitochondrial particles to hydroperoxides results in the generation of chemiluminescence (12). Finally the chemiluminescence observed in brain homogenates obtained from hypoxic rats is believed to originate from lipoperoxidation accompanying hypoxia (13).

The methodology in the current study is similar to that used by Boveris et al. (5) who demonstrated that hepatic chemiluminescence accompanies free radical-induced lipoperoxidation produced by infusion of ethyl and *t*-butyl hydroperoxides into the portal vein. Chemiluminescence was observed with infusion of as little as 12 μmol/min. The degree of chemiluminescence was proportional to the amount of hydroperoxide administered, with a 30-fold increase produced by 108 μmol/min. Chemiluminescence decreased within 10–15 min after discontinuing the infusion.

Our data demonstrate significant differences in the time-course and extent of chemiluminescence in the phenobarbital-induced rat when halothane and chloroform are compared. Stability of the preparation in the absence of lipoperoxidation was observed for 150 min in the two animals anesthetized only with pentobarbital, as well as in all rats during the 30-min control periods (irrespective of whether they were to receive chloroform or halothane).

Do these data relate to differences in the histologic changes produced by the two anesthetics? Histologic examination of phenobarbital-induced rats showed hepatic centrilobular necrosis after chloroform administration; rats given halothane demonstrated only minor histologic changes (10). The present study has demonstrated that halothane and chloroform are not associated with the same pattern of light emission, suggesting that there are major differences in the mechanism by which the two drugs interact with the liver in this model. It is likely that this is a consequence of the differential effects of halothane and chloroform on glutathione stores, a phenomenon that significantly influences the in vivo effects of these two agents on the hepatic cell membrane.

Cellular damage produced by lipoperoxidation requires the accumulation of a sufficient quantity of reactive intermediates (8). The ability of glutathione to scavenge such compounds may ameliorate this damage. Brown (8) has shown that both halothane and chloroform produce increases in diene conjugates. Diene conjugates (compounds with alternating single and double bonds) are products of lipoperoxidation; their presence indicates that this process is occurring but does not necessarily allow estimation of the extent of lipoperoxidation. In the phenobarbital-treated rat, administration of halothane has no effect on glutathione concentration, whereas chloroform produces marked reductions of this scavenger (10). It is likely that halothane's preservation of glutathione stores is associated with (a) a significantly smaller increase in hepatic chemiluminescence and (b) a longer delay preceding the onset of this increase in light output when compared with chloroform.

In summary, continuous in vivo measurements of hepatic chemiluminescence have demonstrated significant differences between chloroform and halothane both in the time of onset and the magnitude of hepatic chemiluminescence. These findings, possibly reflecting differing degrees of lipoperoxidation related to the effects of the two anesthetics on hepatic glutathione stores, are a likely explanation for considerably diminished hepatotoxicity of halothane compared with that of chloroform.

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Continuous Alfentanil Infusion for Extracorporeal Shock Wave Lithotripsy of Gallbladder Stones

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CONNELLY NR, WEINSTOCK AD. Continuous alfentanil infusion for extracorporeal shock wave lithotripsy of gallbladder stones. Anesth Analg 1990;70:299–302.

Extracorporeal shock wave lithotripsy has recently been introduced in clinical trials for the treatment of cholelithiasis. General anesthesia, epidural anesthesia, and intravenous opiates have been used in the anesthetic management of patients undergoing this procedure. This report details our anesthetic management, which was used in 23 patients who underwent 27 procedures, and presents three illustrative cases. A continuous infusion of alfentanil and a 0.625–2.5-mg dose of droperidol were administered to the patients who were easily arousable during the procedure, and were able to cooperate with positioning change requests. Our patients did not develop apnea, hemodynamically significant bradycardia, or chest wall rigidity. One patient became nauseated, and one patient experienced a hypotensive episode that was unheralded by a change in respiratory rate, heart rate, or oxygen saturation. The patients were comfortable throughout the procedure, alert upon arrival to the postanesthesia care unit, and satisfied with this technique. A continuous infusion of alfentanil can be successfully used for the management of patients undergoing biliary lithotripsy.

Key Words: ANESTHETICS, INTRAVENOUS. ANESTHESIA, BILIARY TRACT LITHOTRIPSY.

Extracorporeal shock wave lithotripsy (ECSWL) is used in the treatment of renal calculi, and has recently been introduced in the United States, through clinical trials, for the treatment of radiolucent cholelithiasis (1,2), with the possible benefits of avoiding surgery and postoperative morbidity. Patients are placed in contact with an electrode-containing water cushion that produces a shock wave. The wave is transmitted through body tissues and when it reaches the stone, shearing forces are produced, and the stone is disintegrated. The shocks are triggered by the electrocardiogram.

Many different methods of anesthesia, including general anesthesia, epidural anesthesia, spinal anesthesia, intercostal blocks (3), and, most recently, interpleural anesthesia (4), have been described for renal ECSWL. General anesthesia, epidural anesthesia, and intravenous opiates have been used in the anesthetic management of patients undergoing biliary lithotripsy (2), a procedure that can be quite uncomfortable (5). At our institution, biliary lithotripsy is under investigation for the treatment of cholelithiasis. To facilitate successful gallstone localization by ultrasound, methods of anesthesia must limit patient movement, as well as maintain patient comfort. Alfentanil, a narcotic with a rapid onset and short duration of action (6,7), offers some advantages over other possible methods of anesthesia for the management of patients undergoing biliary lithotripsy. We present here the data from 23 patients treated with this technique who underwent 27 ECSWL procedures, and detail three illustrative cases.

Case Reports

Case 1

A 45-yr-old man presented for biliary lithotripsy. The patient had no significant past medical history aside from symptomatic cholelithiasis. The physical and laboratory examinations were normal. The patient received no premedication, was brought to the lithotripsy van (a trailer connected to the hospital that is equipped with an anesthesia machine and capabilities for full invasive monitoring), and placed in the prone position. Intravenous access was established and oxygen via nasal cannula was administered. Monitors included electrocardiography, noninvasive

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blood pressure, and pulse oximetry. Droperidol (0.625 mg) and alfentanil (5 μg/kg) were administered. An alfentanil infusion was begun at 1 $\mu g \cdot kg^{-1} \cdot min^{-1}$. The patient required an additional two boluses of 5 μg/kg, at 15 and 45 min, and was very comfortable throughout the 3.5-h procedure. The infusion was discontinued 10 min before the end of the procedure. Upon moving from the lithotripsy machine to the stretcher, the patient experienced nausea which was successfully treated with an additional 1.25 mg of droperidol. The patient was alert and comfortable upon arrival in the postanesthesia care unit.

Case 2

A 45-yr-old man, with no significant past medical history, was brought to the lithotripsy van for ECSWL. Monitoring, as in case 1, was applied and intravenous access was secured. Droperidol (1.25 mg) was given, alfentanil (5 μg/kg) was given as a bolus, and an alfentanil infusion was begun at 0.5 $\mu g \cdot kg^{-1} \cdot min^{-1}$. Because of difficulty in localizing the gallstones by ultrasound, the procedure took 4.5 h. The patient required two additional boluses of 5 μg/kg at 1 and 2 h into the procedure because of generalized discomfort. He also received a total of 3 mg of midazolam at the beginning of the procedure, in 1-mg increments, because of agitation. The infusion was stopped 15 min before the end of the procedure, and the patient stated that he was comfortable throughout the entire procedure.

Case 3

A 46-yr-old man presented with a 1-yr history of right upper quadrant colic. He had a history of hypercholesterolemia and hypertension, for which he was taking 50 mg of metoprolol twice a day (baseline treated blood pressure was 110/80 mm Hg). The patient was positioned, an intravenous cannula was placed, and monitors were applied. The end-tidal CO_2 monitor was connected, via a plastic connection, to the nasal cannula. The patient was given 2.5 mg of droperidol and 5 μg/kg of alfentanil, and then begun on an alfentanil infusion of 0.5 $\mu g \cdot kg^{-1} \cdot min^{-1}$. Because of discomfort, the patient required two additional boluses: one of 5 μg/kg with the infusion increased to 1 $\mu g \cdot kg^{-1} \cdot min^{-1}$ at 45 min into the procedure; and a second bolus 30 min later of 2.5 μg/kg with the infusion remaining at 1 $\mu g \cdot kg^{-1} \cdot min^{-1}$. Forty-five minutes after the second bolus, the patient's blood pressure was noted to be 65/45 mm Hg, and the patient was minimally arousable. Immediately before this, the patient's oxygen saturation was 97%, the P_{ETCO_2} was 54 mm Hg, and the respiratory rate was 11 breaths/min. The patient was placed in the Trendelenberg position, the alfentanil infusion was discontinued, and 400 μg of intravenous naloxone was given, while 100% O_2 was administered via a facemask. The oxygen saturation remained above 94%, while 400 mL of lactated Ringer's solution was administered intravenously over a 10-min period. The blood pressure returned to normal, the patient regained full consciousness, and the few remaining shocks were administered without restarting the alfentanil infusion. Shortly after arrival in the postanesthesia care unit, the patient's systolic blood pressure was 65 mm Hg. The patient was comfortable and responsive to commands, was breathing at a rate of 12 breaths/min, and was maintaining an oxygen saturation of 100%. One liter of lactated Ringer's solution was administered intravenously for 0.5 h, with a subsequent rise in the blood pressure. A 12-lead electrocardiogram was obtained, and was unchanged from the pre-ECSWL electrocardiogram. The patient did well after this episode, and was discharged from the hospital on the day after the ECSWL.

Discussion

Biliary lithotripsy is performed with the use of three different types of devices (1). At our institution, the Dornier multipurpose lithotripter (MPL 9000), located some distance from the main operating room, is utilized. A maximum number of 1500 electrocardiogram-triggered shocks is given per treatment, with each session lasting from 1.25 to 4.5 h. Although a number of anesthetic approaches can be used, each has relative disadvantages. Because the technique mandates the patient being placed in the prone position, most anesthesiologists administer general anesthesia to these patients via a tracheal tube. This has the potential for both the adverse pulmonary effects of mechanical ventilation in the prone position and dislodgement of the tracheal tube when changing patient position. Regional techniques necessitate a high sensory level, with the possible complications of hypotension, local anesthetic toxicity, and too high a level. To limit patient motion, regional techniques would require additional intravenous supplementation. We were able to manage these patients successfully using solely intravenous sedation and analgesia. To maintain this level of comfort, a continuous infu-

Table 1. Dose of Alfentanil Used

Patient	Weight (kg)	Duration of ECSWL (h)	Alfentanil total dose (μg)	($\mu g \cdot kg^{-1} \cdot h^{-1}$)
1[a]	125	3.5	11,000	25
2	98	4.5	12,250	28
3	80	2.25	7,000	38
4	97	1.25	2,750	23
5	96	4.5	11,000	25
6	70	2	2,950	21
7	107	1.25	7,200	53
8[b]	90	1.75	3,700	24
9[a]	125	3.25	11,000	27
10[b]	90	1.5	5,500	41
11	72	1.5	1,500	14
12	61	1.5	4,600	50
13	66	1.5	6,500	65
14	57	1.5	2,075	24
15	65	1.5	2,000	21
16	88	1.5	2,650	20
17[c]	89	2	5,500	31
18[c]	89	1.5	3,650	27
19	97	2.5	2,500	12
20[c]	89	2.25	1,450	6
21	100	2.25	7,200	32
22	70	2.5	2,950	17
23	85	2.25	7,500	39
24	50	1.5	3,000	40
25	75	1.5	2,125	19
26	72	2	5,000	35
27	57	1.5	4,600	53

ECSWL, extracorporeal shockwave lithotripsy.
[a,b,c] Identical superscripts indicate repeat procedures in the same patient.

sion technique seemed ideal. Alfentanil infusions have been previously used in spontaneously breathing patients (8,9), and have been shown to provide hemodynamic stability (10). Because of its quick onset and short duration of action (11,12), we chose to use alfentanil in this setting.

After positioning the patient and placement of monitors, droperidol (0.625–2.5 mg) and a loading dose of 5 μg/kg of alfentanil were administered. Simultaneously, an alfentanil infusion of 0.5 $\mu g \cdot kg^{-1} \cdot min^{-1}$ was begun. If the patient became uncomfortable, an additional bolus of 2.5–5 μg/kg was given, and the infusion was increased in increments of 0.25–0.5 $\mu g \cdot kg^{-1} \cdot min^{-1}$. The alfentanil infusion did not need to be turned higher than 1 $\mu g \cdot kg^{-1} \cdot min^{-1}$ in any of our patients, and can be discontinued 5–15 min before the end of the procedure. The dosages of alfentanil given to the patients in our series are shown in Table 1.

A continuous infusion technique offers the benefit of a steady plasma concentration with maintenance of patient comfort and the ability to adjust the plasma level rapidly as the level of stimulation changes (13). An infusion pump (Bard Harvard Mini Infusor, Harvard Apparatus Co., Inc., South Natick, Mass.) was used to administer the drug, which enables the user to adjust the infusion in increments of 0.25 $\mu g \cdot kg^{-1} \cdot min^{-1}$ and alerts the user to the total amount of drug administered.

Dose-dependent ventilatory depression occurs with alfentanil. Delayed respiratory depression has also been reported with alfentanil infusion techniques (14,15). The respiratory rate was maintained above 10 breaths/min in all of our patients and the oxygen saturation was maintained above 94%. The addition of droperidol to alfentanil has not been studied, although droperidol does not appear to increase the depressant effect upon ventilation when used in combination with fentanyl (16,17).

Biliary tract spasm has been associated with the use of narcotics (18). Given the nature of the underlying disease process in these patients, if an episode of biliary colic occurs, the narcotics must be considered as a possible etiologic agent. However, none of the patients in our series experienced biliary spasm related to the alfentanil infusion.

As both biliary tract manipulation and alfentanil itself can cause nausea and vomiting, patients were given droperidol (19) (0.625–2.5 mg) at the beginning of the procedure. None of the patients experienced nausea during the procedure. One patient became nauseated upon moving from the lithotripsy machine to the stretcher; this was successfully treated with an additional 1.25-mg dose of droperidol.

The vagotonic effects of alfentanil can cause a slowing of the pulse rate. As ECSWL is triggered by the electrocardiogram if the heart rate becomes excessively slow, the duration of the procedure will be prolonged. If this is the case, and if no contraindications exist, the administration of an anticholinergic drug will decrease the time required for the lithotripsy. An occasional patient in our series, approximately 5%, received 0.2 mg of glycopyrrolate for this reason.

In summary, a continuous infusion of alfentanil can be successfully used for the management of patients undergoing biliary lithotripsy. Patients were easily arousable throughout the procedure, and were able to cooperate with positioning change requests. Our patients did not develop apnea, bradycardia, or chest wall rigidity. One patient became nauseated upon moving to the stretcher. One patient experienced a hypotensive episode unheralded by a change in respiratory rate, heart rate, or oxygen saturation. Possible explanations for this hypotension include intravascular volume depletion secondary to the patient's *non per os* status, alfentanil-induced vagal tone, α-blockade from the droperidol administration, increased vagal tone induced by the lithotripsy shock waves on the peritoneum, or a combination of the above-mentioned factors. The patients were very alert upon arrival to the postanesthesia care unit and stated that they were comfortable during the procedure. The patients were satisfied with the level of analgesia, and were pleased that they were able to avoid general anesthesia. As with all administrations of anesthesia, this method requires a high level of vigilance. We present this report at a time when biliary lithotripsy is in its infancy in this country, and has the potential to become an important noninvasive method of treating gallstones. As this practice becomes more popular, anesthesiologists will be increasingly called upon to participate in the care of these patients.

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Review Article

Pro- and Anticonvulsant Effects of Anesthetics (Part I)

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An epileptic seizure has been defined as a sudden alteration of central nervous system (CNS) function resulting from a high-voltage electrical discharge. This discharge may arise from an assemblage of neurons in either cortical or subcortical tissues. The spread of this excitatory activity to the subcortical, thalamic, and brainstem centers corresponds to the tonic phase of the seizure and loss of consciousness (1). In contrast, myoclonic activity refers to a series of rhythmic or arrhythmic muscular contractions (2). Depending on the electroencephalographic (EEG) findings, myoclonus is divided into epileptic and nonepileptic activity (3). Nonepileptic myoclonus originates from the brainstem or spinal cord and is due to either loss of cortical inhibition (4) or to impaired function of spinal interneurons (3,5). Without EEG monitoring, it is extremely difficult to determine whether abnormal-appearing seizurelike muscle movements are due to epileptiform activity or nonepileptic myoclonia.

Many anesthetic and analgesic drugs have been reported to cause seizure activity clinically (Table 1, A). Interestingly, many of these same drugs have also been shown to possess anticonvulsant properties (Table 1, B). In an effort to explain deficiencies with Guedel's original stages of anesthesia, Winters and colleagues (6,7) proposed a multidirectional continuum of anesthetic states (Figure 1). For example, some agents (e.g., diethyl ether) traverse both CNS excitation (stages I, II) and depression (stage III). Others (e.g., halothane, ultrashort acting barbiturates) progress directly from stage I to III, whereas still others (e.g., nitrous oxide [N_2O], enflurane, ketamine, and narcotics [8]) induce a stage II cataleptoid CNS excitation, which on occasion progresses to myoclonia or generalized convulsions. Based on EEG studies in cats, Winters suggested that both excessively disorganized (stage II) and decreased reticular-formation activity (stage III) result in unresponsiveness to painful stimuli and amnesia, consistent with

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Table 1. Anesthetics and Analgesics Reported to Cause and/or Suppress Seizure Activity in Humans

A. Proconvulsants	B. Anticonvulsants
Nitrous oxide	Halothane
Halothane	Enflurance
Enflurane	Isoflurane
Isoflurane	Thiopental
Morphine	Etomidate
Meperidine	Diazepam
Fentanyl	Lorazepam
Sufentanil	Midazolam
Methohexital	Ketamine
Etomidate	Propofol
Diazepam	Local anesthetics
Ketamine	
Propofol	
Local anesthetics	

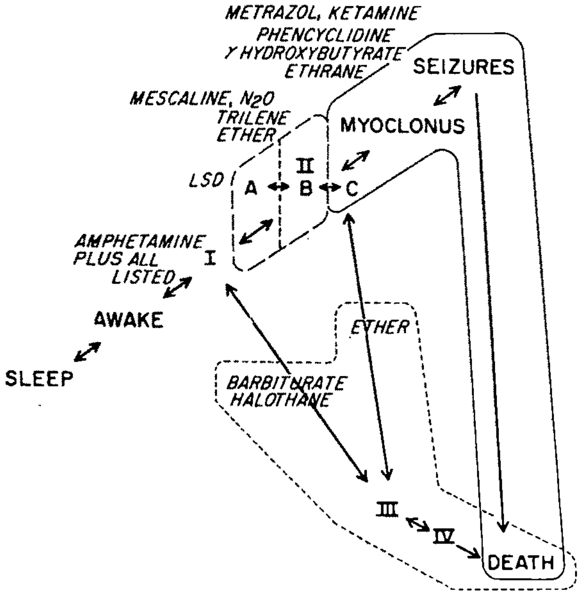

Figure 1. Winter's proposed scheme of reversible progression of CNS states induced by various anesthetic and excitant agents. Stages I, II, A, B, C, myoclonus, and seizures indicate CNS excitation, whereas stages III and IV indicate CNS depression. (From Winters WD, Ferrer-Allado T, Guzman-Flores C, Alcaraz M. The cataleptic state induced by ketamine: a review of the neuropharmacology of anesthesia. Neuropharmacology 1972;11:303–15, with permission.)

the anesthetic state. Although both epileptic and anesthetic states possess similar features regarding arousal and memory, the categorization proposed by Winters fails to adequately explain the actions of those anesthetics that appear to possess both proconvulsant and anticonvulsant properties (Table 1). For example, ketamine, an alleged stage II anesthetic which Winters believed to be contraindicated in epilepsy, has been successfully used to terminate status epilepticus (9,10), and conversely, methohexital, a stage III agent, has been used in the diagnostic activation of epileptogenic foci (11,12).

To properly categorize the various anesthetic agents with respect to their effects on the seizure threshold, there are several important factors to consider. The first consideration is the patient population studied. For example, methohexital, in its current formulation (Brevital; Eli Lilly, Indianapolis, Ind.), will only produce epileptiform activity in patients with known seizure disorders (11,12). A second factor to consider is the method of proconvulsant and anticonvulsant documentation. This had led to confusion in the literature regarding the effects of some anesthetics and analgesics on CNS activity. Fentanyl-induced seizures have been described clinically without the support of EEG documentation (13–15). In some instances, these convulsivelike muscle movements may be due to nonepileptic myoclonus.

For most drugs used in anesthesia, subsequent EEG evaluation during their administration has helped to clarify whether or not a particular agent is truly epileptogenic in patients. However, for certain anesthetics, such as ketamine (16), the origin of epileptiform activity involves subcortical neuronal pathways. In humans, subcortical seizures are detected only with implanted EEG depth electrodes, not by standard surface leads. Thus, a third important factor to consider in determining whether or not an anesthetic possesses proconvulsant or anticonvulsant properties is the type of EEG recording electrodes (surface or depth) used during its evaluation.

In this review article, we have attempted to analyze the evidence for proconvulsant and anticonvulsant activity of anesthetics and analgesics. This information has been evaluated with respect to (a) patient population (epileptic or nonepileptic); (b) documentation of pro- and anticonvulsant activity (EEG study or clinical report); and (c) method of EEG analysis (surface or depth electrodes).

Inhalation Anesthetics

Volatile Agents

Enflurane. Abnormal movements consisting of twitching of individual muscle groups, and even tonic-clonic activity, were frequently observed during the early clinical evaluation of enflurane (17,18). Subsequent EEG recordings in normal patients demonstrated epileptiform activity (19,20) and grand mal seizure patterns (21) (Table 2). These findings with enflurane have also been confirmed in patients with temporal lobe epilepsy during both electrocortico-

Table 2. Proconvulsant Effects of Inhalation Anesthetics in Humans

Agent	Population	Seizure documentation: Clinical report	Seizure documentation: EEG study	Type of EEG electrodes used in study	References
Nitrous oxide	Nonepileptic	+	−	Surface	58, 64, 96
	Epileptic	−	−	Depth	16
Halothane	Nonepileptic	−	−	Surface	60–62
	Epileptic	−	−	Surface	63
Enflurance	Nonepileptic	+	+	Surface	17–21, 26, 28
	Epileptic	+	+	Surface/depth	22–25
Isoflurane	Nonepileptic	−	−	Surface	75–78
	Epileptic	N/A	N/A		
Sevoflurane	Nonepileptic	−	−	Surface	86
	Epileptic	N/A	N/A		
Desflurane (I-653)	Nonepileptic	N/A	N/A		
	Epileptic	N/A	N/A		

+, presence of seizures; −, absence of seizures; EEG, electroencephalographic; N/A, information not available.

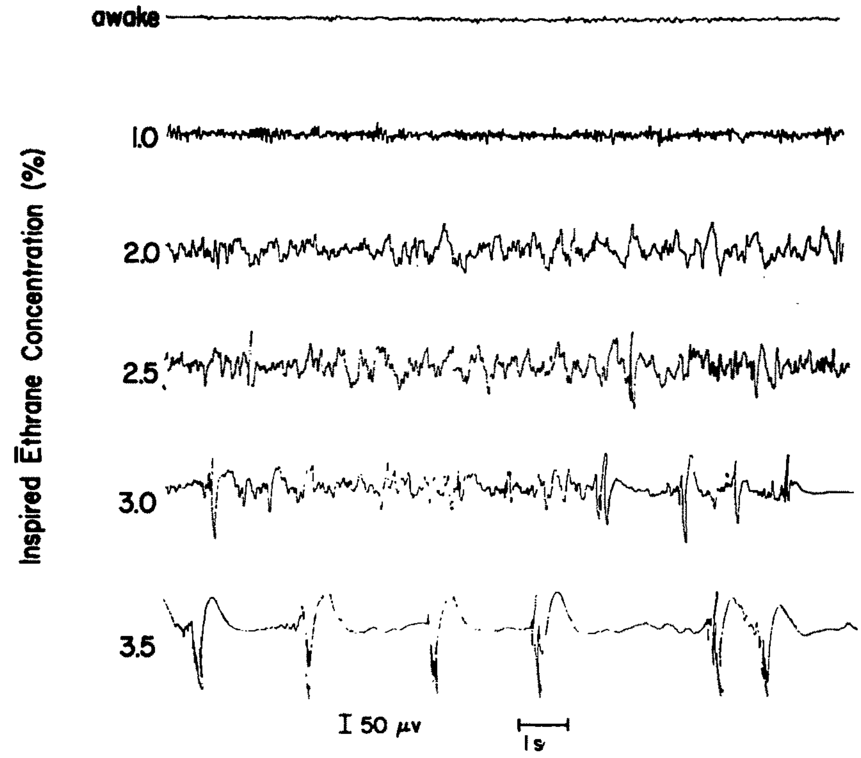

Figure 2. Electroencephalographic patterns with increasing concentrations of enflurane. (From Neigh JL, Garman JK, Harp JR. The electroencephalographic pattern during anesthesia with Ethrane: effects of depth of anesthesia, $Paco_2$, and nitrous oxide. Anesthesiology 1971;35:482–7, with permission.)

graphic (22–24) and depth electrode recordings (25). In ten healthy volunteers, grand mal seizure patterns were precipitated by auditory, visual, and tactile stimulation at end-tidal enflurane concentrations of 3%–6% (26). This has also been reported during otic microsurgery (27). In both normal (28) and epileptic (25) patients, increasing depth of enflurane anesthesia is characterized by the appearance of high-voltage spikes, with the subsequent development of spike waves—spike and dome activity with intermittent periods of burst suppression (Figure 2). In contrast to other volatile anesthetics, these burst suppression patterns are thought to represent an excitatory event (29).

The ability of enflurane to produce seizure or EEG spiking activity is influenced by both its concentration and the $Paco_2$ (25,28). At a normal $Paco_2$ level, spiking is maximal at inspired enflurane concentrations of 2%–3%. Higher $Paco_2$ concentrations reduce spiking activity (22). Interestingly, N_2O does not affect the tendency of enflurane to produce spiking activity (28). With an alveolar enflurane concentration between 2.5% and 3%, hyperventilation to an average $Paco_2$ of 22 torr produced an increase in the frequency, magnitude, and synchrony of the spiking activity in epileptics (25). This technique has since been used to activate silent epileptogenic foci intraoperatively, to delineate the site of seizure activity before discrete surgical excision (23,24).

Conversely, with an enflurane concentration of 3.5%, the addition of CO_2 to the inhaled gas produced a decrease in magnitude and frequency of spiking activity (25). At an end-tidal CO_2 of 91 torr, spiking was not observed despite the fact that the enflurane alveolar concentration was increased to 4%. The relationship between enflurane concentration, $Paco_2$, and epileptiform activity was further evaluated in a volunteer study that demonstrated that the minimum epileptogenic enflurane concentration was approximately 1% lower when the $Paco_2$ was 20 torr (vs normocarbia), and 1% higher when $Paco_2$ was 60 torr (26).

Postoperative seizure activity related to enflurane administration has also been reported, primarily in nonepileptic patients. These seizures may occur in the immediate postanesthetic period (30–33), within hours of surgery (34), and possibly as long as 3–9 days later (35,36). In a few instances the patients were either epileptic (33) or had a familial history of seizure disorders (36). In other reports, only transient (37,38) or prolonged (39) myoclonic activity has been observed in otherwise conscious patients after enflurane. Whether or not these reports of postoperative seizurelike activity in normal patients are truly related to enflurane administration is unclear. Transient surface EEG spike (30) or seizure (23,36) activity has been reported postoperatively, which was absent on follow-up EEG studies. However, in volunteers exposed to 9.6 MAC hours of enflurane, only diffuse nonepileptiform EEG changes were observed using surface electrodes for 6–30 days after anesthesia (40). Half of these volunteers had exhibited both clinical and EEG seizure activity during enflurane anesthesia. In an animal study (41), high-amplitude spikes were recorded from depth electrodes in the thalamus for up to 15 days after exposure to enflurane. Therefore, one cannot exclude the possibility that after enflurane anesthesia there is actual subcortical epileptiform activity.

Various drugs have been reported to either enhance enflurane-induced spiking activity or lower its threshold. Both diazepam (30) and small doses of thiopental (42) were found to intensify enflurane-induced seizures in humans. Larger doses of thiopental diminished seizure activity. In cats, enhanced enflurane-induced seizure activity has been demonstrated with the concomitant administration of diazepam, thiopental, methohexital, ketamine (43), and scopolamine (26). Conversely, in dogs, scopolamine significantly decreased enflurane-induced spiking activity (44). This may represent species variability to the CNS effects of scopolamine. Using depth electrodes in cats, Darimont and Jenkins (43) demonstrated that diazepam lowered the threshold for spiking activity by producing a leftward shift in the curve relating spiking frequency and enflurane concentration. In view of these contrasting findings, it remains unclear whether diazepam or thiopental should be used to treat perioperative seizures associated with enflurane anesthesia.

A variety of studies in animals have examined the mechanism of enflurane-induced hyperexcitability. It is unclear as to whether enflurane induces epileptogenic activity by inhibiting synapses (43,45) or by stimulating excitatory neuronal transmission (46). In investigations performed on cats with depth electrodes, it was reported that the seizure activity originated from the limbic system (amygdala and hippocampus) and midline thalamic nuclei (26,43,46). The subcortical origin for the epileptogenic properties of enflurane was further supported by the finding in rats that local cerebral glucose use (LCGU) in the limbic system was preserved or increased, whereas LCGU in many other structures was significantly decreased during deep enflurane anesthesia (47). However, similar alterations in limbic system metabolism also have been reported for anesthetics without epileptogenic properties (e.g., chloral hydrate [48], phenobarbital [49], and halothane [50,51]). Furthermore, in a recent study in rats (52), the authors suggested that intercortical and corticothalamic pathways are metabolically activated during enflurane seizure activity.

In more than 300 patients with seizure disorders, the frequency of convulsivelike EEG activity during enflurane anesthesia was less compared with the previous sleep and awake EEGs of these epileptics (53). Furthermore, enflurane has been reported to inhibit seizure activity arising from epileptogenic foci (54,55). In animals, enflurane suppresses convulsions induced by electroshock, pentylenetetrazol, bicuculline, and penicillin (56,57). In amygdaloid-kindled cats, it was reported that both low (1.5%) and high (3.5%) concentrations of enflurane suppressed seizure activity (57). In children, successful termination of status epilepticus has been demonstrated with

Table 3. Anticonvulsant Effects on Inhalation Anesthetics in Humans

Agent	Anticonvulsant documentation: Clinical report	Anticonvulsant documentation: EEG study	Type of EEG electrodes used in study	References
Nitrous oxide	−	−	Surface	85
Halothane	+	+	Surface	53, 66
Enflurane	+	+	Surface	53, 54
Isoflurane	+	+	Surface	74, 82, 83, 85
Sevoflurane	N/A	N/A		
Desflurane (I-653)	N/A	N/A		

+, successful termination of status epilepticus reported; −, failure to eliminate seizures reported; EEG, electroencephalographic; N/A, information not available.

enflurane (53) (Table 3). The disappearance of EEG seizure activity was evident 20 min after induction and no further convulsive activity was noted during recovery. Despite these anticonvulsant findings, enflurane has a propensity for inducing epileptiform activity during anesthesia, especially when high concentrations are administered in the presence of hypocarbia.

Halothane. Halothane alone has not been reported to cause convulsions in humans (Table 2). In the few reports (58,59) of halothane-related seizures, N_2O was also administered. Electroencephalographic monitoring in normal patients had not revealed epileptiform activity during halothane anesthesia (60–62). However, nonspecific EEG slowing and rare sharp wave activity (attributed to the persistence of halothane and its metabolites) was seen in volunteers during the first week after 13–14 MAC-hours of halothane administration (60). In three epileptic patients, brief periods (<7 s) of bilateral atypical and polyspike waves were noted during emergence from halothane, but were not associated with clinical seizure activity during the perioperative period (63). Mild transient clonus has been observed after halothane anesthesia (37). Epileptic activity has been reported in cats given a high concentration of halothane (7%); however, cerebral blood flow and metabolism is also markedly altered at this concentration (64). Although depth electrodes have revealed occasional hippocampal spikes in cats (46), evoked spikes were not detected during halothane anesthesia in dogs subjected to loud hand-clapping in the presence of hypocapnia (65).

Inhaled anesthetics, including halothane, have been recommended for treatment of continuous seizures refractory to conventional intravenous anticonvulsant agents (66). Successful termination of resistant status epilepticus in children has been demonstrated with halothane (53) (Table 3). In these cases, the disappearance of spikes and waves was evident within 20 min. No seizures were noted after recovery. These potent anticonvulsant effects combined with the lack of clinically important cerebral excitatory findings for halothane would suggest that it does not possess proconvulsant properties.

Isoflurane. When administered alone, isoflurane has not been found to cause EEG or clinical seizure activity in anesthetized patients (Table 2). In the reported cases of isoflurane-related seizures (67–69), N_2O was also administered. In two of these cases, abnormal myoclonic movements starting intraoperatively and lasting into the early postanesthetic period were the only evidence of seizure activity (67,68). Furthermore, one of these patients was conscious throughout the recovery period (67). In contrast to the reported convulsions after enflurane (23,30,36), the postoperative EEG was normal in both reports. Alternative explanations for these seizurelike movements include nonepileptic myoclonus (3,70) and/or the so-called withdrawal phenomena from N_2O (71,72).

In another case report (69), isoflurane-N_2O anesthesia was associated with tonic-clonic activity early during inhalational induction on two separate occasions. Before the second anesthetic, EEG studies were entirely normal. With EEG monitoring during the second induction, spike and wave forms were recorded during the clinical seizure and both ceased after administration of thiamylal. In this case, the finding that the spiking activity appeared with induction but did not continue during maintenance or reappear during recovery implies that N_2O may have precipitated the seizure activity (73). Furthermore, N_2O alone has been associated with clinical seizures during induction (58,64), whereas isoflurane's anticonvulsant properties may have prevented further seizures during the maintenance and recovery periods (73,74).

In unpremedicated volunteers, induction of isoflurane anesthesia is characterized by low-voltage fast EEG activity that progresses toward high-voltage slow wave activity at 1 MAC. Bursts of slow high-voltage activity separated by electrical silence are noted at 1.5 MAC, with electrical silence at ≥2 MAC (75–77). Epileptic or spiking patterns do not appear, nor can they be evoked by lowering the Pa_{CO_2} or by introduction of auditory and visual stimuli (75,77). Unpremedicated volunteers did not demonstrate clinical or EEG evidence of seizure activity during isoflurane-N_2O inhaled induction (77). In premedicated patients undergoing inhaled induction with isoflurane and N_2O (78), spikelike wave complexes lasting 1–2 s were seen when end-tidal isoflurane was increased above 2.5% and end-tidal CO_2 was intentionally lowered. In cats (79,80), isoflurane was associated with high-voltage synchronous spikes but not seizures. In dogs subjected to loud hand-clapping in the presence of hypocapnia (65), isoflurane caused spontaneous spiking without seizure activity. It is unknown whether or not isoflurane, with or without N_2O, will activate epileptogenic foci in patients with preexisting seizure disorders. However, seizurelike movements have not been reported during isoflurane anesthesia in epileptic patients.

Isoflurane has well-characterized anticonvulsant properties. In animals, isoflurane produced complete suppression of drug-induced convulsions (81–84). In patients with status epilepticus resistant to conventional therapy, isoflurane-O_2 produced rapid cessation of seizures with a burst suppression pattern at inspired concentrations ranging from 0.5% to 3.0% (74,82,83,85) (Table 3). When isoflurane was discontinued after exposures lasting 1–54 h, seizures recurred in 50% of the patients studied. These reports combined with the absence of EEG and clinical seizure activity during studies of its administration alone indicate that isoflurane is a potent anticonvulsant in humans.

Investigational volatile agents. Sevoflurane and desflurane (I-653) are newly synthesized volatile anesthetics that are structurally similar to enflurane and isoflurane. The low solubility of both agents makes them potentially useful when rapid awakening is desired (e.g., outpatient anesthesia) (86,87). In unpremedicated volunteers, successive incremental inspired sevoflurane doses of 1%, 2%, and 4% produced EEG patterns that contrasted with those commonly observed during the administration of most anesthetics (86). In light planes, an increase in both frequency (10–14 Hz) and amplitude, associated with unconsciousness, was observed in all subjects receiving sevoflurane. At deep levels, slower, low-voltage, 5–8-Hz activity also appeared; however, the predominant 10–14-Hz activity persisted with a further increase in amplitude. Interestingly, a separate exposure of the same volunteers to an initial inspired sevoflurane concentration of 4% initially produced high-amplitude, rhythmic slow waves (2–3 Hz) that coincided with loss of consciousness (86). The latter EEG pattern was dominant for 2–3 min, and then was replaced by a pattern identical to that observed during exposure to a lower concentration of sevoflurane. These findings are opposite to the traditional view that the greater the arterial blood level of anesthetics, the slower the EEG activities. No EEG or motor evidence of seizure activity has been reported during anesthesia with sevoflurane (Table 2). It is unknown whether or not sevoflurane will activate epileptogenic foci in patients with preexisting seizure disorders.

Recently, EEG activity during anesthesia with desflurane was compared with isoflurane and enflurane in swine (87). In this report, desflurane produced EEG waveforms and quantitative EEG values almost identical to those of isoflurane at equipotent concentrations. At low end-tidal concentrations (0.8 MAC) of desflurane, paroxysmal fast activity was occasionally noted. Higher concentrations produced progressive slowing of the EEG, and isoelectricity was observed at 1.6 MAC. No EEG or motor evidence of seizure activity was noted during desflurane administration. Furthermore, when these animals were exposed to either hypocapnia or external auditory stimuli, they did not demonstrate seizure activity during either desflurane or isoflurane anesthesia. In contrast, EEG and motor seizures occurred during hypocapnia with and without auditory stimuli in animals given 3.2% enflurane. The EEG effects of desflurane have not been investigated in humans. It is also unknown if sevoflurane and desflurane possess anticonvulsant properties. Further studies regarding the effects of these new volatile agents on CNS electrical activity in humans are clearly needed.

Nitrous Oxide

Animal studies would suggest that N_2O stimulates brain metabolism when combined with other anesthetics (88–91). Withdrawal convulsions have been described in mice after short exposures to both normobaric (0.6–0.9 atm) and hyperbaric (1.2–1.6 atm) N_2O (92,93). Volunteers exposed to hyperbaric (1.5 atm) N_2O exhibited muscle rigidity, jerking movements, and occasional hyperactivity alternating with apparent relaxation (94). In contrast, mice exposed to high pressures of helium and/or 100% O_2 did not display convulsions when removed from these gases (93).

Hypersynchronous epileptoid EEG activity and an increase in reticular-formation neuronal activity was reported during N_2O anesthesia in cats studied with depth electrodes (95). However, EEG studies performed in patients receiving N_2O alone have not revealed seizure activity (Table 2). In unpremedicated epileptic (16) and nonepileptic (96) patients studied with depth electrodes and surface EEG, respectively, 70% N_2O produced fast activity (15–35 Hz) but no evidence of seizure activity. The epileptic patients

Table 4. Proconvulsant Effects of Opioid (Narcotic) Analgesics in Humans

Agent	Population	Seizure documentation: Clinical report	Seizure documentation: EEG study	Type of EEG electrodes used in study	References
Morphine	Nonepileptic	+	–	Surface	114, 118, 120
	Epileptic	+	N/A		115
Meperidine	Nonepileptic	+	+	Surface	99–101, 103, 104, 111
	Epileptic	N/A	N/A		
Fentanyl	Nonepileptic	+	–	Surface	13–15, 114, 128–130, 134–136, 139, 142
	Epileptic	N/A	N/A		
Sufentanil	Nonepileptic	+	–	Surface	131, 132, 135, 137, 143
	Epileptic	N/A	N/A		
Alfentanil	Nonepileptic	+	–	Surface	133, 135, 138
	Epileptic	N/A	N/A		

+, presence of seizures; –, absence of seizures; EEG, electroencephalographic; N/A, information not available.

exhibited restlessness and hallucinations, whereas the nonepileptics remained unresponsive to stimuli. Although no convulsionlike withdrawal phenomena were reported, the fast EEG activity persisted for up to 1 h after discontinuation of N_2O (96). In volunteers, diffuse paroxysmal bursts of high-voltage theta activity were observed immediately after cessation of N_2O 30% (71). There appears to be only one case report, without EEG documentation, in which N_2O alone precipitated convulsions (Table 2). In a child who convulsed during a halothane-N_2O induction, subsequent inductions with halothane alone did not precipitate a seizure, whereas use of N_2O alone was associated with seizurelike movements (58,64).

N_2O alone has never been demonstrated to possess anticonvulsant properties in humans (Table 3). In one patient with refractory convulsions, 60% N_2O alone slowed but did not eliminate tonic-clonic or EEG seizure activity (85). In animals, N_2O was found to elevate the local anesthetic seizure threshold (97) and to reduce the frequency of EEG spiking activity during enflurane anesthesia (98). N_2O remains the oldest and most widely used anesthetic in clinical practice. In view of this long-standing record of safety and the available evidence regarding its cerebral stimulatory effects, its epileptogenic potential appears to be extremely low.

Intravenous Analgesics

Opioid (Narcotic) Analgesics

Meperidine. Meperidine neurotoxicity is well known and is manifest clinically as shakiness, tremors, myoclonus, and seizures (99) (Table 4). This neuroexcitement is attributed to its *N*-demethylated metabolite normeperidine (100,101). The half-life of normeperidine (14–21 h) is significantly longer than that of meperidine (3–4 h). Thus, with repeated or continuous meperidine administration, normeperidine can accumulate, leading to neurotoxicity (99–101). The risk of precipitating convulsions is theoretically greater with chronic oral administration because it produces lower meperidine and higher normeperidine blood levels due to extensive first-pass metabolism (102). However, seizures have occurred after both chronic oral (99,103) and intramuscular (100,104) administration. Myoclonus generally precedes the seizures, and both resolve over several days with discontinuation of meperidine administration (101,103).

Anticonvulsants (e.g., phenytoin [105], phenobarbital [106]) and phenothiazines (e.g., chlorpromazine [107]) have been demonstrated to increase the conversion of meperidine to normeperidine in humans. In mice, concomitant administration of promethazine and meperidine has been shown to be synergistic in inducing seizures (108). Concomitant therapy with either anticonvulsants (103) or phenothiazines (104,109) may have been a contributing factor in some reports of seizure activity after oral or parenteral meperidine administration.

The EEG pattern after intravenous administration of a single high dose (400 mg) of meperidine is characterized by primarily high-voltage delta waves, similar to that reported for other narcotics (110). However, in otherwise healthy patients in whom seizures occurred after repeated meperidine administration, EEG studies have revealed diffuse slow activity and epileptiform discharges (99,111) (Table 4).

Patient subgroups that appear to be more susceptible to the neurotoxicity associated with chronic meperidine therapy include (a) patients with renal failure in whom the normeperidine half-life is prolonged (34 h) due to decreased metabolism and excretion (100,103), and (b) patients with advanced malignancy (100,101) or sickle cell anemia (112), both of whom receive progressively larger doses of meperidine due to the development of tolerance. Seizure-like movements have not been reported in epileptic patients during either acute or chronic meperidine administration. Furthermore, it is unknown whether or not acute or chronic meperidine use will activate epileptogenic EEG foci in patients with preexisting seizure disorders.

Meperidine has demonstrated the lowest safety margin for convulsions of all narcotics studied. In dogs, EEG seizure activity was induced with an average intravenous meperidine dose (20 mg/kg) that was only 2.2 times greater than the mean effective intravenous dose (9 mg/kg) for surgical analgesia (8). In mice, naloxone can only partially block the convulsions induced by normeperidine, whereas meperidine-induced seizures are completely blocked by prior administration of naloxone (113). Neither meperidine nor normeperidine has ever been shown to possess anticonvulsant properties. Within the range of meperidine doses used clinically to supplement general or regional anesthetic techniques, the proconvulsant effects of the drug appear to be of little concern. However, seizures may result from normeperidine accumulation after prolonged meperidine administration (e.g., patient-controlled analgesia), especially in patients with renal failure, sickle cell, and cancer.

Morphine. Morphine alone has never been demonstrated to produce seizure activity in humans after intravenous administration. High-dose morphine (1–2 mg/kg, IV) during open-heart surgery was associated with progressive slowing of EEG activity and an increase in low-frequency amplitude. No epileptiform activity was noted (114). Electroencephalographic investigations have not been performed in epileptic patients during high-dose morphine administration. However, a tonic-clonic seizure was reported after administration of epidural morphine to a known epileptic (115) (Table 4). There was a 6-h delay between epidural administration and the onset of seizure, consistent with the known kinetics of morphine in the cerebrospinal fluid (116,117). A convulsion has also occurred after intrathecal morphine in a nonepileptic cancer patient (118). These reports suggest a subcortical origin for morphine-induced seizures. Electrophysiologic studies in rats support this concept as morphine causes disinhibition of the pyramidal cells of the hippocampus, leading to seizure discharges (119). A grand mal seizure in a 14-yr-old boy occurred 90 min after 20 mg of intramuscular morphine and 0.4 mg of scopolamine were administered (120). A prodrome of intense itching was experienced by the patient, indicating that morphine probably contributed to the seizure activity, although the well-known excitatory CNS effects of scopolamine may have been an additional contributing factor in this case. Withdrawal seizures have been reported clinically, predominantly in neonates born to heroin-addicted mothers (121).

DeCastro et al. (8) found that an average morphine dose of 180 mg/kg, IV, was required to precipitate EEG seizure activity in dogs. This was 72 times greater than the mean effective intravenous dose (2.5 mg/kg) for surgical analgesia. In rats, higher systemic doses of morphine produce epileptiform patterns and behavioral convulsions that are not reversed by opiate antagonists (122). Seizures have also been demonstrated after intracerebroventricular administration of morphine in rats (123,124) and after intrathecal administration of morphine in dogs (125) and rats (126). Although the cerebroventricular-induced seizures are naloxone reversible (124), the intrathecal morphine-induced tonic-clonic movements were not naloxone reversible (126). These findings suggest that the proconvulsant actions of high doses of morphine in animals are mediated by both opiate (e.g., mu) and nonopiate (e.g., γ-aminobutyric acid) receptor mechanisms (122,127).

Morphine alone has never been demonstrated to possess anticonvulsant properties in humans. In rabbits, intravenous morphine terminated bicuculline- and picrotoxin-induced EEG and behavioral seizures (127). In rats, intravenous morphine delayed the onset of pentylenetetrazol- and flurothyl-induced seizures (122). Although intravenous morphine in high doses has both pro- and anticonvulsant properties in animals, the doses of the drug used in clinical practice appear to have little effect on the seizure threshold. This is especially true with noncerebrospinal fluid routes of morphine administration.

Fentanyl and its analogues. There have been several reports of grand mal seizure-like motor behavior in patients after administration of low (100–200 μg) (14,15,128,129) to moderate (2250–2500 μg) (13,130) doses of intravenous fentanyl. This phenomena has also occurred after sufentanil (40–150 μg, IV [131, 132]) and alfentanil (1500 μg, IV [133]) administration (Table 4). None of the patients had a history of seizure disorder and their EEGs after surgery were unremarkable. Unfortunately, in these case reports, the authors did not have the benefit of EEG recording during the seizurelike event.

Surface EEG recordings in patients treated with high intravenous doses of fentanyl (60–150 μg/kg [114,134–136]), sufentanil (15 μg/kg [135,137]), or alfentanil (>50 μg/kg [135,138]) are characterized by high-voltage slow delta waves. Similar EEG findings were also demonstrated in patients receiving low-to-moderate doses of fentanyl (139). Except for sporadic isolated sharp waves noted in two of the high-dose fentanyl studies (134,136), these EEG investigations did not detect any epileptic spike waves or other abnormal patterns (Table 4). The significance of these sharp waves is not known as they were nonepileptiform in appearance and never became generalized (134). Although they have not been related to tonic-clonic movements, similar sharp waves also have been noted during the administration of other drugs known to be epileptogenic (e.g., phencyclidine [140], intrathecal metrizamide [141]). Whether sharp waves represent an EEG equivalent of a CNS stimulatory action or merely EEG artifact remains unclear. Although tonic-clonic movements associated with their administration have not been reported in epileptic patients, EEG studies have never been performed in this population during anesthesia with fentanyl or its analogues alone.

Abnormal motor activity resembling epileptic convulsions has occurred in the absence of cortical seizure activity on simultaneous EEG recordings made during low-dose (500–600 μg, IV) fentanyl (132,142) and sufentanil (1.3 μg/kg, IV) (143) administration. Yet, seizurelike movements were not observed during EEG studies in patients treated with high doses of fentanyl and its analogues. There are several possible explanations for these observations. The abnormal movements observed after low-to-moderate doses of fentanyl or sufentanil could be due to nonepileptic myoclonus produced by the interaction of these narcotics with opiate receptors leading to blockade of cortical inhibitory pathways. This would allow lower CNS centers in the brainstem and/or spinal cord to display altered excitability (4,142). Patients treated with higher doses of fentanyl and its analogues may have failed to exhibit these seizurelike myoclonic movements because the plasma opioid levels were high enough to depress both higher and lower CNS centers. In one report, nonepileptic myoclonus was probably responsible for the seizurelike motor activity observed after recovery from low-dose fentanyl administration (128). In addition, this patient also received etomidate, an anesthetic that produces nonepileptic myoclonic activity (144), which occasionally persists into the postoperative period (145,146).

An alternative explanation is that these movements represent an exaggerated form of narcotic-induced rigidity (142). Rigidity can occur after low doses of fentanyl (147) and high-dose alfentanil inductions have produced rigidity involving all extremities that closely resembles seizures in volunteers (148). Recent studies have suggested that rigidity may involve neurochemical mechanisms in the striatonigral pathways similar to Parkinson's disease (149–151). Thus, exaggerated rigidity could have been responsible for the seizurelike movements observed after low-dose sufentanil administration (131). In these two cases, one patient had a history of Parkinson's disease, and the other patient was receiving chronic metoclopramide therapy. Metoclopramide inhibits cerebral dopaminergic pathways and can produce extrapyramidal signs (152,153).

The tonic-clonic movements reported with administration of low-to-moderate doses of fentanyl and sufentanil could also be due to subcortical seizure activity. Electroencephalograph-documented cortical seizures have been induced by high-dose fentanyl (8,154,155) and sufentanil (156) in animals. The EEG seizures in rats were accompanied by decreases in LCGU in cortical structures and relative increases in LCGU in the subcortical limbic system (hippocampus, amygdala, claustrum) (154,155), an area rich in opioid receptors. In humans, subcortical seizures are not detected by surface EEG leads, and EEG studies with depth electrodes are required to confirm or reject the hypothesis that fentanyl and sufentanil cause seizures in humans (155).

Fentanyl and its analogues alone have never been demonstrated to possess anticonvulsant properties in either humans or animals. However, during fentanyl administration with droperidol and N_2O (neuroleptanesthesia), EEG monitoring in epileptic patients did not demonstrate an increase in spiking activity compared with their baseline EEG studies (53). In a study of 104 patients receiving neuroleptanesthesia, no EEG or clinical signs of seizures were observed during or after neuroradiologic examinations with intrathecal metrizamide, a known convulsant (141). As suggested by DeCastro et al. (8), these findings appear to indicate that droperidol may offer some protection against narcotic-induced neuroexcitation.

Whether the seizurelike movements reported during clinical administration of fentanyl and its analogues originate from epileptogenic or nonepileptogenic mechanisms is unclear. All currently available clinical and EEG evidence appears to favor either nonepileptic myoclonus or exaggerated rigidity as the most likely explanation. However, further studies regarding the neurochemical mechanisms of narcotic-induced rigidity and the effects of progressively higher doses of fentanyl and its analogues on electrical activity in the limbic system are needed.

Summary

Many inhaled anesthetics and intravenous analgesics have been alleged to produce both proconvulsant and anticonvulsant activity in humans (Table 1). The reasons for these contrasting actions on the CNS are poorly understood at the present time. However, biologic variability plays an important role in determining individual patient's responses to anesthetic and analgesic drugs. In addition, variations in the responsiveness of inhibitory and excitatory neurons to the central depressant effects of these drugs could also explain these apparently conflicting data. Depending on the brain concentration, centrally active drugs may produce differing effects on the CNS inhibitory and excitatory neurotransmitter systems. The availability of increasingly powerful magnetic resonance imaging techniques to provide noninvasive information about tissue chemistry (e.g., neurotransmitters and citric acid cycle metabolites) and positron emission tomography to noninvasively evaluate CNS drug-receptor interactions should lead to a more in-depth understanding of the in vivo effects of anesthetics and analgesics on the CNS.

In the second part of this review article, we discuss the pro- and anticonvulsant effects of the sedative-hypnotics, local anesthetics, and other anesthetic adjuvant drugs.

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Clinical Reports

Differences in Epidural Morphine Requirements Between Elderly and Young Patients After Abdominal Surgery

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Key Words: PAIN, POSTOPERATIVE. ANALGESICS, MORPHINE. AGE FACTORS, POSTOPERATIVE PAIN. ANESTHETIC TECHNIQUES, EPIDURAL—morphine.

Epidural administration of morphine is an established technique for the relief of postoperative pain (1–7). It has been our clinical impression, along with that of others, that elderly patients have greater pain relief with epidural morphine than do younger patients (8). The purpose of this study was to determine the validity of our clinical impression by studying the degree of pain relief after a single equal dose of epidural morphine in two groups of patients, an elderly group, aged 65 yr and older, and a younger group, aged 50 yr or younger. The plasma concentrations of morphine achieved after epidural administration were also determined within a subset of each group to assess any pharmacokinetic differences.

Materials and Methods

Two groups of patients were studied: group 1, 20 patients aged 65 yr or older, and group 2, 17 patients aged 50 yr or younger. All patients were scheduled for elective major abdominal surgery. All patients were ASA physical status I to III. Approval for the study was obtained from our institution's research committee and informed consent was obtained from each patient.

Group 1 patients were not premedicated. Group 2 patients received no premedication or 0.15 mg/kg of diazepam orally 1 h preoperatively at the discretion of the attending anesthetist.

A lumbar epidural catheter was placed before the induction of general anesthesia. All patients had indwelling arterial cannulas for continuous blood pressure monitoring and blood sampling. The induction and maintenance of anesthesia were accomplished without the use of narcotics. Patients were given 3.0 mg of *d*-tubocurine before receiving 3–5 mg/kg of thiopental until the loss of lash reflex; this was followed by 1.5 mg/kg of succinylcholine for tracheal intubation. Anesthesia was maintained with nitrous oxide in oxygen with the addition of isoflurane or enflurane as required. The choice of neuromuscular blocking agent was left to the discretion of the attending anesthetist. At the end of the surgical procedure, muscle relaxation was reversed. Extubation was done in the operating room before transfer of patients to the recovery room.

A single epidural injection of preservative-free morphine (0.5 or 1.0 mg/mL) was given shortly after induction of anesthesia, based on a dose of 0.07 mg/kg or 5.0 mg/70 kg, respectively. The volume of solution injected was made up to a total of 10 mL with preservative-free normal saline.

All patients were monitored in the recovery room with electrocardiogram and blood pressure monitoring for a minimum of 18 h. The respiratory rate was assessed every 10 min for the first 90 min, then every 30 min until 10 h from the time of the epidural morphine injection. Thereafter the respiratory rate was recorded hourly.

Postoperative pain relief was judged effective if the patient did not request any analgesic supplementa-

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Table 1. Demographic Data

	Group 1	Group 2
Number	20	17
Age (yr)[a]	76.9 ± 9.04	36.3 ± 10.9
Male/female	14/6	10/7[b]
Mean dose of morphine[a] (mg)	4.31 ± 0.76	4.53 ± 0.86[b]

[a] Mean ± SEM.
[b] No significant difference vs group 1.

Table 2. Operative Procedures

	Group 1	Group 2
Gastric	5	1
Small bowel	1	2
Colon	13	12
Miscellaneous	1	2
Total	20	17

tion within 12 h after the administration of epidural morphine; it was judged ineffective if the patient did request supplementation. Recovery-room nursing staff acted as blinded observers. All patients received standard postoperative care (i.e., deep breathing, coughing, incentive spirometry, and turning in bed) and were directly asked, "Do you have pain?" Analgesic supplementation was provided immediately upon request.

Plasma morphine levels were determined in the first eight patients in each group. Serial blood samples were drawn; the first was a baseline sample drawn just before epidural morphine administration, and repeated samples were taken 2, 5, 10, 15, 30, 60, 90, and 120 min after morphine injection.

Blood samples were initially stored at 4°C, centrifuged as quickly as possible after collection, and the plasma stored at −20°C until free plasma morphine levels were determined using a modified version of the extraction method of Kim and Katz (9). A simple one-step solvent-solvent extraction of drug was followed by quantitation using high-performance liquid chromatography with electrochemical detection. The concentration of morphine was determined from a calibration curve carried through the extraction procedure providing peak height ratio (drug/internal standard nalorphine) versus drug concentration. Measurements of morphine concentrations as low as 2 ng/mL from a sample volume of 0.2 mL were easily achieved. Calibration curves were linear over the range 6.25–200 ng/mL plasma with a mean correlation coefficient of $R^2 = 0.9993$. Intraassay and interassay coefficients of variation for morphine at 25 ng/mL are ±4.5% ($n = 7*4$) and ±5.7% ($n = 28$), respectively. The analytical recovery is 33.3% ± 3.16% for morphine over the specified calibration curve range and 77.2% ± 0.9% for nalorphine (internal standard) at 50 ng/mL.

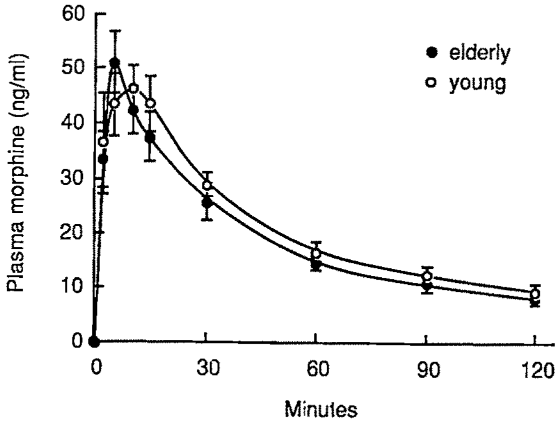

Figure 1. Plasma morphine concentrations (ng/mL) from 0 to 120 min after epidural morphine (0.07 mg/kg) in elderly and young patients. No significant differences between groups.

Differences in systemic absorption of epidural morphine between the two groups were assessed by two-way analysis of variance for repeated measurements. Dunnet's test was used to determine whether there were significant differences in morphine concentrations within each group from control. Fisher's exact two-tailed test was used to test for significant differences in the effectiveness of analgesia between groups. A P value of <0.05 was considered statistically significant.

Results

Table 1 summarizes demographic data for patients in each group. Table 2 lists the surgical procedures for patients in both groups.

Plasma Morphine Levels

Peak plasma morphine concentrations averaging 51.1 ± 5.8 ng/mL at 5 min were achieved in group 1; in group 2 peak plasma morphine concentrations averaging 46.3 ± 4.2 ng/mL were achieved at 10 min (Figure 1). Two-way analysis of variance shows plasma morphine concentrations did not differ significantly between groups ($P > 0.05$).

Effectiveness of Pain Relief

Elderly patients had significantly better pain relief than did younger patients (Table 3). Only 4 of 20

Table 3. Efficacy of Pain Relief

	Effective	Ineffective
Group 1 ($n = 20$)	16	4
Group 2 ($n = 17$)	6[a]	11[a]

[a] $p < 0.05$.

elderly patients required supplemental analgesia, whereas 11 of 17 young patients needed supplementation after receiving standardized doses of morphine epidurally. Among the four elderly patients needing supplementation two requested additional analgesia within minutes of arrival in the recovery room. Both patients received 8 mL of 0.125% bupivacaine in increments, obtained rapid relief, and did not require further supplementation of local anesthetic or narcotic during their overnight stay. The remaining two elderly patients required supplemental epidural morphine in addition to epidural bupivacaine for satisfactory analgesia. In the younger patient population, the majority of patients requesting supplementation did so within the first 90 min of arrival at the recovery room. Supplementation with local anesthetic alone was effective for only a short period of time. All young patients required additional epidural morphine for satisfactory analgesia.

The duration of analgesia was consistently prolonged in the elderly group. Of the patients not requiring supplementation before 12 h, the next shortest interval was 21 h from the time of initial morphine injection. Most elderly patients received their first supplementation toward the end of their first postoperative day. In two patients, aged 87 and 98 yr, no further medication for pain relief was ever requested following vagotomy and small bowel resection, respectively, (Figure 2).

No patients in our study experienced late respiratory depression. The lowest recorded respiratory rate was 15 breaths/min for the elderly patients and 12 breaths/min for young patients. Two of the 20 elderly patients had nausea and vomited. Both had hemicolectomies, and the likelihood that nausea and vomiting were attributable solely to epidural morphine is questionable. One young patient who had a hemicolectomy experienced nausea and vomiting. Two young patients reported pruritus but did not require any form of treatment. No elderly patients complained of pruritus. All patients in both groups, with the exception of two young patients, had indwelling bladder catheters inserted at the start of their procedures. Both these patients required insertion of Foley catheters in the recovery room for urinary retention.

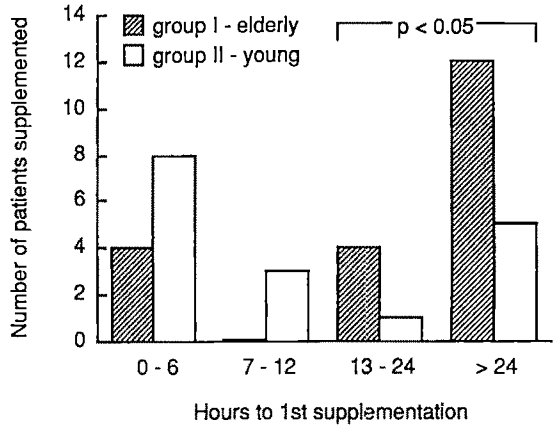

Figure 2. Hours to the first request for supplementation for analgesia after epidural morphine (0.07 mg/kg). Elderly patients achieved significantly more effective pain relief ($P < 0.05$ Fisher's exact two-tailed test).

Discussion

Our study showed no significant differences between groups in the systemic absorption of morphine from the epidural space. Absorption occurs immediately and is rapid, reaching peak plasma concentrations in group 1 of 51.1 ± 5.18 ng/mL by 5 min and 46.3 ± 4.2 ng/mL in group 2 by 10 min. Chauvin et al. (10), using higher doses of epidural morphine (0.2 mg/kg), achieved peak concentrations of 50.3 ± 20.5 ng/mL at 14 ± 9 min. Similar peak concentrations in our study, despite smaller doses, may reflect an increased sensitivity in our method of measurement. Nordberg et al. (11) studied the clinical pharmacokinetics of 2, 4, and 6 mg of epidural morphine. Peak plasma concentrations occurred at 15 min, and mean peak plasma concentration increased with increasing dosage. Our peak plasma concentrations for comparable doses were higher, again possibly reflecting different detection methods. We could not demonstrate any dose-response effect. Peak plasma concentrations similar to those in our study were seen by Weddel and Ritter (12) with comparable morphine doses of 5.0 mg/70 kg body wt, also using high-performance liquid chromatography and electrochemical detection methods of analysis.

Despite initial significant serum concentrations of morphine after epidural administration, these concentrations declined to very low levels (<20 ng/mL) by 90 min. Berkowitz et al. (13) speculate that morphine plasma levels of 50 ng/mL are required for moderate analgesia. The prolonged effective analgesia after epidural morphine results from morphine's action on receptors at the spinal cord level.

In this study, epidural morphine was administered immediately after the induction of anesthesia. This allowed for the longest possible interval between the time of administration and the emergence from anesthesia to establish analgesia. This is particularly beneficial to the elderly patient, for whom smooth emergence from anesthesia without attendant hemodynamic changes associated with pain is beneficial.

Although Ready et al. (8) also showed an inverse correlation between age and effective epidural morphine dose, there are major differences between their study and ours that deserve close consideration. All patients in Ready's study had abdominal hysterectomies, whereas our study patients had major abdominal surgery, including upper abdominal surgery, where postoperative pain is generally considered more severe. In Ready's study, the dose of epidural morphine administered was determined by patient age (15–44 yr, 5 mg; 45–65 yr, 4 mg; 66–75 yr, 3 mg; >75 yr, 2 mg). Our dose of epidural morphine was administered based on body weight, as 0.07 mg/kg for both the elderly and the younger groups. We were interested in determining whether a single dose of epidural morphine would supply effective analgesia from emergence of anesthesia for at least 12 h. Our data support our initial impression that elderly patients achieve more effective pain relief than do young patients given equal doses of morphine. Ready's study supplies data on the effective accumulative 24-h dose of morphine.

Ready et al. speculate that the reduced dose requirements in older patients might be due to an age-related greater effect from the systemically absorbed morphine. However, the plasma morphine concentrations in our patients fell far below what is believed to be the approximate level required for moderate postoperative analgesia 90 min after administration.

Age is one of many factors that might play a role in determining the efficacy of the method chosen to obtain pain relief (8,14–18). Belleville et al. (14), for example, found that elderly patients obtained greater relief of postoperative pain than younger patients after intramuscular morphine or pentazocine. Sherman and Robillard (15) also reported decreased pain perception in the elderly , and Kaiko et al. (17) found the duration of analgesia to be longer in elderly than in young patients after standardized doses of intramuscular morphine. They suggested that morphine is cleared more slowly in the elderly.

The reasons for the difference in the dose requirements in producing effective epidural analgesia with morphine in old and young patients are unclear, although several have been suggested. Morphine concentrations in cerebrospinal fluid after epidural injection are higher in the elderly (19). Reduced elimination through intravertebral foramina may account for these higher levels. The progressive decline in the number of neurons within the central nervous system with increasing age has also been suggested as part of the explanation for the differences in pain relief seen in elderly patients receiving epidural bupivacaine (18). Decreased concentrations of opiate receptors in specific areas of rat brain with increasing age have been demonstrated but without changes in opiate receptor binding affinity. This suggests the possibility of a decrease in spinal cord opiate receptors as an explanation for superior pain relief. The decline in receptor numbers may result in a relative increase in concentration of drug at the site of action and therefore increased effect. An alternative explanation may include adjustment of the endogenous opioid system in the elderly.

In summary, the effectiveness of a single dose of epidural morphine (0.07 mg/kg) for postoperative analgesia after major abdominal surgery was compared between groups of young and elderly patients. Elderly patients achieved statistically more effective pain relief than did young patients. Plasma morphine levels after the single dose of epidural morphine were measured in the first eight patients in each group. No significant differences were found in the plasma concentrations of morphine between groups.

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Accidental Epidural Narcotic Overdose

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Key Words: ANESTHETIC TECHNIQUES, EPIDURAL. ANALGESICS, MORPHINE.

The effectiveness of epidural administration of opioids for alleviation of postoperative pain is well recognized. We report the effects of a large dose of epidural morphine accidentally administered to a patient naive to opioids.

Case Report

The patient was a healthy 39-yr-old woman (weight 54 kg, height 169 cm), scheduled for elective minor orthopedic surgery. Six hours after an uneventful lumbar epidural anesthetic with 15 mL of 0.5% bupivacaine, the patient complained of pain and was given 4 mg of morphine epidurally. This dose was repeated 4 h later.

Twenty-three hours postoperatively (time 0, Figure 1), the patient again complained of pain and was mistakenly given 400 mg of morphine epidurally (10 mL of morphine, 40 mg/mL, in a solution containing 0.5 mg/mL of sodium pyrosulfite meant for intravenous use). The error was not immediately noted. Twenty-five minutes after the injection, however, the patient became somnolent and developed respiratory depression with peripheral and central cyanosis. The lungs were immediately ventilated with 100% oxygen using a face mask and 0.2 mg of naloxone was given intravenously with restoration of respiration and awareness. Blood pressure was 120/80 mm Hg with a pulse rate of 96 beats/min.

During the next 9 h, the patient was treated intravenously with repeated doses of 0.2 mg of naloxone, and in the following 17 h with continuous intravenous infusion of 0.004 mg/mL of naloxone at rates adjusted to respiration, level of consciousness, and acid-base status in arterial blood. Cumulative doses of naloxone are shown in Figure 1.

Six hours after the epidural injection of 400 mg of morphine, the error was confirmed.

For 20 h after the injection, the patient remained drowsy but easily aroused. The respiratory frequency was 5–12 breaths/min and could be accelerated by verbal command. $\mathrm{Pa{CO_2}}$ measured 1, 7, 10, 13, and 28 h after the injection was 48.8, 72, 64.5, 54, and 42.8 mm Hg, respectively. Blood pressure averaged 114/70 mm Hg (range 100/60 to 130/80) mm Hg, and mean heart rate was 88 beats/min (range 80–100). The electrocardiogram 1 h after the injection was normal apart from a corrected Q-T interval of 0.438 s. Upon aspiration through the epidural catheter, 1 mL of clear fluid with, it was found, a concentration of glucose of 0.0 mmol/L could be drawn from the catheter. The absence of glucose indicated that the 1 mL was not cerebrospinal fluid and intrathecal displacement of the catheter had not occurred. Venous blood samples drawn 1, 8, 19, and 27 h after the injection, examined by a specific radioimmunoassay (1), had morphine concentrations of 1988, 183, 39, and 42 ng/mL, respectively.

Urinary retention and motor or sensory dysfunction were not observed in this patient. When the error was confirmed 6 h after the injection, temperature and pain modalities evaluated on several occasions with ice-water and pin-prick were normal.

Administration of naloxone was terminated after 26 h. The patient was discharged from the hospital 4 days later without sequelae.

Discussion

To our knowledge, epidural morphine administration in this quantity in an opioid-naive patient has not been reported previously. Accidental administration of two doses of 50 mg of epidural morphine within a 10-h period in a healthy 24-yr-old woman without subsequent respiratory depression has been reported (2). In another report, inadvertent intrathecal injection of 20 mg of morphine was followed by respiratory as well as neurological depression (3).

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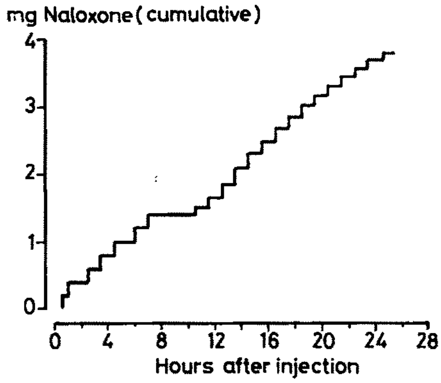

Figure 1. Cumulative doses of naloxone administered intravenously during treatment with respiratory depression after accidental epidural injection of 400 mg of morphine.

In our present case, the initial respiratory depression was undoubtedly caused by systemic absorption of morphine from the epidural space, but was initially interpreted as caused by a conventional dose of 4 mg of epidural morphine, and so only limited doses of naloxone were administered. Infusion of 10 $\mu g \cdot kg^{-1} \cdot h^{-1}$ of naloxone has been used to prevent the respiratory changes after epidural morphine (4), but caution has been recommended when naloxone is given to reverse the depressant effects of opioids, particularly when these have been administered in high doses (5).

No significant clinical effects on cardiovascular function were detected. Also, no effects on motor function or sensory modalities were detected in the present case. The subarachnoid space, the spinal cord, and the spinal nerves are, as mentioned by Gissen et al. (6), essentially desheathed nerve preparations; and possible local anesthetic-type actions of opioids will not be limited by lack of diffusion through a nerve sheath. Thus, high concentrations of fentanyl and sufentanil may exert a weak local anesthetic-type action as desheathed rabbit vagus nerves (6). Acalovschi et al. (7) reported sensory and motor blockade with subarachnoid injections of 5% meperidine in patients undergoing short surgical operations on the perineum.

The observations in the present case suggest, however, that no clinically important local anesthetic-type actions of morphine on peripheral nerves can be expected. However, we may have overlooked discrete changes in motor function or sensory modalities in the first 6 h after the injection.

In this hospital, preservative-free morphine intended for extradural or intradural injection is available in 10-ml ampules containing 0.4 or 0.8 mg of morphine per milliliter. The preparation used in this report, containing 40 mg of morphine per milliliter in a 10-ml ampule meant for intravenous use, has now been replaced with a smaller ampule with a totally different label.

In summary, 400 mg of morphine was accidentally injected epidurally into an opioid-naive patient. Respiratory depression developed 25 min later, and the patient was intravenously treated with a total of 3.8 mg of naloxone during a 26-h period. Vital signs were otherwise unaffected. No local anesthetic-type actions of morphine were observed and the patient was discharged from the hospital without sequelae.

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Prolongation of Postoperative Epidural Sufentanil Analgesia With Epinephrine

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Key Words: PAIN, POSTOPERATIVE—epidural sufentanil with epinephrine. ANESTHETIC TECHNIQUES, EPIDURAL—sufentanil with epinephrine.

Sufentanil is a highly lipid-soluble, potent opioid that effectively relieves postoperative pain after cesarean section when given epidurally (1). Its high lipid-solubility confers the properties of rapid onset and theoretically low potential for delayed respiratory depression, both of which appear to be distinct advantages over the less lipid-soluble and more water-soluble morphine. However, the duration of action of epidural sufentanil is only 4–6-h (1), compared with the 23–26-h duration of epidural morphine (2). The addition of vasoconstrictors such as epinephrine to local anesthetic solutions significantly prolongs their duration of action (3,4). An early report suggested that the duration of epidural sufentanil postoperative analgesia may also be prolonged by the addition of epinephrine (5). However, data in that study were inconclusive because of the small number of observations made. We speculated that with the addition of a larger dose of epinephrine in a somewhat larger study population, we might be able to demonstrate a statistically significant difference between sufentanil and sufentanil plus epinephrine given epidurally.

Methods

Twenty parturients between the ages of 18 and 45 yr, ASA physical status I or II, who had chosen epidural anesthesia for elective cesarean section were included. The parturients were randomly divided into two groups of 10 patients each. The study received institutional approval and written informed consent was obtained from each patient. The study was carried out in a randomized, double-blinded, prospective fashion. Anesthesia for cesarean delivery was provided with 0.5% bupivacaine injected via an epidural catheter placed at the L2-3 or L3-4 level. Epinephrine given epidurally was limited to 15 μg included in a 3-mL test dose. Adjunctive intravenous (IV) drugs given intraoperatively were limited to $\leq$3 mg midazolam, $\leq$2.5 mg droperidol, and $\leq$100 μg fentanyl. The epidural catheter was left in place after the operation.

Upon requesting analgesia in the recovery room, group 1 patients (n = 10) were cautiously given 50 μg sufentanil epidurally, whereas group 2 patients (n = 10) received 50 μg sufentanil plus 300 μg epinephrine epidurally. All epidural agents were diluted to a total of 10 mL volume with sterile preservative-free normal saline. Both patient and investigator were blinded as to which test solution was administered. The epidural catheter was then removed.

Intensity of pain was assessed using a 100-mm visual analog scale. The patient was asked to rate her pain intensity immediately before the administration of epidural opiate, 2.5 min after its administration, and then every 5 min until she considered her analgesia adequate. Vital signs including blood pressure, pulse, and respiration were recorded at the same time. Adequate analgesia was defined as >90% pain relief from baseline levels using the visual analog

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Table 1. Onset and Duration of Analgesia

	Group 1 (min)	Group 2 (min)
Time to onset of:		
50% pain relief (min)	6.2 ± 2.7	9.5 ± 6.3
90% pain relief (min)	12.0 ± 4.8	13.5 ± 7.8
Duration (min)	266.7 ± 80.2	348.7 ± 77.8[a]

Values represent mean ± SD.
[a]Significant at $P \leq 0.05$.

scale. The duration of analgesia was measured as the time between onset of adequate analgesia to the first request for additional pain medication. All patients were observed for at least 12 h after epidural sufentanil for the appearance of side effects such as nausea and pruritus. These side effects were treated when the patients requested such treatment. All patients were informed of these possible side effects when informed consent was obtained and knew that treatment was available if desired. The patients were also monitored for respiratory depression for 12 h after epidural sufentanil. The patients were questioned at the 24-h postoperative visit regarding the appearance of these symptoms. Additionally, the nursing notes and medical administration records were reviewed. Subsequent analgesic requirements over the first 72 postoperative hours, in terms of morphine equivalents, were recorded for each patient. A morphine equivalent is defined as an analgesic equivalent of intramuscular morphine according to the following: 10 mg of intramuscular morphine = 100 mg of intramuscular meperidine = 120 mg of oral codeine phosphate = 15 mg of oral oxycodone hydrochloride.

Demographic data, time required for 50% and 90% pain relief, duration of effective analgesia, total 72-h postoperative analgesic requirements, and hemodynamic changes after injection of test solutions were compared using the Student's *t*-test. The incidence of side effects was analyzed using χ^2 analysis. A *P* value of <0.05 was considered statistically significant.

Results

There were no significant differences in height, weight, or age between the two groups. Epidural sufentanil provided >90% pain relief in all patients studied. Time to onset of analgesia was also not significantly different in the groups at either the 50% or 90% pain relief levels (Table 1). Duration of analgesia was, however, significantly longer in group 2 (Table 1), a mean of 348.7 ± 77.8 min (mean ± SD), than in group 1 (266.7 ± 80.2 min). There was no significant difference between the two groups regarding subsequent analgesic requirement over the first 72 postoperative hours. The incidence of side effects (pruritus, nausea) was similar between the two groups, but there was a significantly higher incidence of side effects that required treatment (diphenhydramine, promethazine) in group 2. Hemodynamic changes, including arterial blood pressure and heart rate after epidural injection, were not significantly different between the two groups.

Discussion

The results of this study suggest that epidural administration of 50 μg sufentanil is a very effective method of providing analgesia after cesarean section. The addition of epinephrine has been shown to prolong spinal anesthesia with local anesthetics (3,4). Although this prolongation is generally thought to be due to decreased vascular uptake of local anesthetic, this may not be the only mechanism. Recent research suggests that adrenergic modulation of spinal cord activity may be an important factor in the transmission of pain information in the spinal cord. Collins et al. (6), using the decerebrate, spinal cord-transected cat model, found that epinephrine suppressed noxiously evoked activity in a wide dynamic range in neurons in the dorsal horn of the spinal cord. Therefore, vasoconstrictors such as epinephrine may act directly on the spinal cord to enhance or prolong analgesia. The postulated role of epinephrine as a modulator of neurotransmission is thus a possible explanation for the prolongation of epidural sufentanil analgesia; however, epinephrine's direct action on the spinal cord does not necessarily explain why the duration of action of the sufentanil is prolonged. This may still be related to changes in the rate of elimination of sufentanil from the spinal cord, epidural spaces, or subarachnoid spaces.

The rather large dose of epinephrine (300 μg) was selected to demonstrate an unequivocal effect, if one existed, on the duration of action of epidural sufentanil. This same dose has been shown to be effective in prolonging spinal anesthesia with local anesthetics (3,4). We were somewhat surprised to find no significant changes in mean arterial pressure or heart rate between the two groups after injection of the respective test solutions. The test solutions were diluted in a 10-mL volume of preservative-free normal saline and injected slowly while vital signs were monitored and the patient observed.

The use of epinephrine to prolong epidural sufentanil has been preliminarily studied with inconclusive results. In six patients Parker et al. (7) found that the addition of 50 μg of epinephrine to 10 μg of sufentanil did not prolong duration of analgesia but did increase the incidence of side effects. However, in addition to studying a smaller number of patients, the doses of both sufentanil and epinephrine were much less than in the present study. Cohen et al. (5) investigated sufentanil for analgesia after cesarean section, comparing IV sufentanil to epidural sufentanil (50 μg) plus an unstated amount of epinephrine and found the duration tended to be longer with epidural sufentanil plus epinephrine. This study did not reach statistical significance, possibly because of the small number of patients in each group. Additionally, any prolongation may have been obscured by the epinephrine that was added to the local anesthetics used for operative epidural anesthesia and not solely to the test dose.

We found a statistically significant prolongation of epidural sufentanil analgesia when epinephrine was added. Therefore, the question is whether the 30% increase in duration of analgesia we observed is clinically advantageous, especially when compared with the usual duration of epidural morphine (the most commonly used agent for this purpose). To answer this question, the practitioner must consider the risks as well as the benefits. The unintentional IV injection of 300 μg of epinephrine is not without risk. One could argue that this risk is greater than the small benefit of an additional 80 min of analgesia. Additionally, there is the risk of IV injection of 50 μg of sufentanil and the potential for significant respiratory compromise. Finally, there is the risk of drug error and contamination associated with mixing drugs.

On the other hand, a study by Van der Auwera et al. (8) that compared sufentanil and morphine administered epidurally demonstrated a better quality of postoperative analgesia with sufentanil with no increased incidence of side effects. In addition, in a further study by Rosen et al. (1), side effects were fewer with epidural sufentanil than with epidural morphine. Finally, the high lipid solubility of sufentanil confers the properties of rapid onset and low potential for delayed respiratory depression. Therefore, whether or not the 30% increase in duration with the use of epidural epinephrine added to epidural sufentanil is clinically significant probably depends on the specific circumstances of a particular case.

Other means of prolonging the duration of epidural sufentanil without adding epinephrine—including epidural sufentanil as a continuous infusion or a repeated bolus technique—need to be compared in further studies.

Postoperative epidural analgesia is indeed profound with sufentanil, and of intermediate duration, but accidental IV injection of even small doses of sufentanil can certainly produce rapid changes in consciousness and respiration. It must be stressed, therefore, that the epidural administration of sufentanil requires close cardiovascular and respiratory monitoring with the immediate availability of oxygen and appropriate resuscitative equipment.

In conclusion, we determined that epinephrine prolonged the duration of epidural sufentanil analgesia after cesarean section by studying two groups of 10 patients each in a randomized double-blinded fashion. Group 1 received 50 μg epidural sufentanil, and group 2 received 50 μg epidural sufentanil plus 300 μg epinephrine. Duration of analgesia was significantly longer ($P < 0.05$) in group 2, with a mean of 348.7 + 80.2 min, than in group 1, with its mean of 266.7 + 80.2 min. There were no significant differences between the groups with respect to time of onset of analgesia or subsequent parenteral narcotic requirement in the first 72 postoperative hours. However, there was a significantly higher incidence ($P < 0.05$) of side effects (pruritus, nausea) requiring treatment in group 2 patients.

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Perioperative Blood Transfusion May Conceal Atypical Pseudocholinesterase

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Key Words: ENZYMES, PSEUDOCHOLINESTERASE. NEUROMUSCULAR RELAXANTS, SUCCINYLCHOLINE—delayed recovery.

The incidence of patients who are homozygous for an atypical pseudocholinesterase enzyme has been estimated at one in 3200 (1). Intubating doses of succinylcholine (1–2 mg/kg) produce a profound neuromuscular blockade in these patients for a period of 4–8 h (2). We report a case of pseudocholinesterase deficiency with prolonged neuromuscular blockade in a young woman who had previously received succinylcholine for general anesthesia without an abnormal response.

Case Report

A 23-yr-old white woman, gravid 2, para 0, at 37-wk gestation was admitted to the hospital for elective cesarean section for breech presentation of a severely hydrocephalic fetus. Her past medical history was remarkable only for left salpingoophorectomy 18 mo previously for ruptured ectopic pregnancy. She denied any problems with general anesthesia at that time. She required no chronic drug therapy. The family history was negative for anesthetic complications. She had no drug allergies. Physical examination revealed an anxious 71.8-kg white woman. A II/VI systolic ejection sound was heard over the aortic outflow tract. Her hemoglobin was 12.4 g/dl.

The patient requested general anesthesia. A rapid sequence induction was accomplished, preceded by 3 mg of *d*-tubocurare, using 300 mg of thiopental and 120 mg of succinylcholine intravenously. Cricoid pressure was applied. The trachea was intubated with a 7.0-mm cuffed endotracheal tube without difficulty. Anesthesia was maintained with 50% N_2O, 50% O_2, and 0.5 MAC isoflurane. Approximately 4 min after skin incision, a viable male infant with severe hydrocephalus was delivered with 1- and 5-min Apgar scores of 3 and 7, respectively. After the cord was clamped 2 g of cefazolin and 250 μg of fentanyl were given intravenously. The patient's vital signs remained stable.

Fifteen minutes after induction, there was no response to supramaximal nerve stimulation at 2 Hz or tetanic stimulation of the ulnar nerve. The patient was normothermic and normocarbic. Preoperative electrolytes and hematocrit were normal. Neuromuscular blockade was verified by stimulation of the opposite ulnar nerve and facial nerves. Surgery finished 45 min after induction with no return of neuromuscular function.

The patient was kept sedated and ventilated and was evaluated every 20 min for return of neuromuscular function using a nerve stimulator. Four hours after induction, muscle strength sufficient for extubation was verified by sustained head lift for 5 s. The trachea was then extubated and the patient recovered without further incident.

A venous blood sample for measurement of plasma pseudocholinesterase levels and dibucaine number was drawn 8 h postoperatively. The former was 2.4 U/mL (normal 7–19 U/mL) and the latter was 15.6 (normal 80). These findings are consistent with a homozygous atypical pseudocholinesterase genotype. Repeated measurements 6 mo postoperatively showed pseudocholinesterase levels to be 2.76 U/mL with a dibucaine number of 22.4.

The patient was questioned again about her previous surgery and anesthetic. She denied any knowledge of complications resulting in prolonged recovery or emergence. Records obtained from her previous hospitalization revealed that the patient was

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operated on 18 mo previously for a ruptured ectopic pregnancy. Review of the anesthesia record for this previous operation at another hospital revealed that a rapid sequence induction was accomplished with etomidate, sufentanil, and succinylcholine (80 mg intravenously). Vecuronium (6 mg) was given 20 min after induction. The record did not mention the use of a nerve stimulator. The operation lasted 125 min. Packed red blood cells (2 U) were administered during surgery to replace intraoperative blood loss. Residual neuromuscular blockade was reversed with neostigmine and atropine. At the conclusion of the case the trachea was extubated. The patient did well postoperatively and showed no signs of residual muscle weakness.

Discussion

This patient had no evidence of a prolonged response to succinylcholine during her first anesthetic. It has been shown that pregnancy decreases pseudocholinesterase levels by 25%–30%, but generally a decrease of this magnitude only prolongs the clinical effects of succinylcholine by a matter of minutes (3,4). The prolonged response to succinylcholine observed with her second anesthetic could not be explained by a pregnancy-induced decrease in enzyme activity.

The intraoperative transfusion of 2 U of packed red blood cells during her first operation may have provided an adequate amount of pseudocholinesterase to metabolize the succinylcholine given. A search of the literature revealed laboratory evidence that pseudocholinesterase activity measured in bank blood averages 87% of initial activity after 21 days of storage in citrate-phosphate-dextrose solution (5). We were able to reproduce these results in our laboratory. Four units of packed red blood cells prepared in citrate-phosphate-dextrose-adenine solution (CPDA-1) were analyzed over a 4-wk period. Pseudocholinesterase activity was quantitatively measured using the DuPont Automatic Clinical Analyzer and the coupled oxidation-reduction reaction described by Gal and Roth (6).

It is known that citrate interferes with the quantitative measurement of pseudocholinesterase activity (7). To determine whether a change in enzyme activity was due to the presence of citrate in processed units or to the alteration of the enzyme over time, serum samples were obtained from the donor units and tested before processing with CPDA-1. Plasma was drawn from the supercentrifuged units immediately after processing, and enzyme activity was determined. The plasma samples from processed units averaged a 25% decrease in activity compared with original serum samples. This immediate decrease in activity is possibly due to the citrate. By repeating enzyme activity measurements over a 4-wk period on plasma taken from the packed red blood cells, it was determined that there was no further significant reduction in enzyme activity compared with the initial value.

The 4 h of profound neuromuscular blockade experienced by this patient at our institution is certainly an expected response to succinylcholine in patients with atypical pseudocholinesterase. It appears that the patient's enzymatic defect may have been masked during the previous anesthetic by the perioperative administration of packed red blood cells.

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Increased Fluid Flow Through the Streamline Intravenous Catheter

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Key Words: EQUIPMENT, CATHETERS.

An intravenous (IV) catheter called the Streamline venous access device (Menlo Care, Palo Alto, Calif.) has been developed and approved by the FDA for use in humans. It is constructed of a new polyurethane-based hydrogel polymer blend known as Aquavene (Menlo Care). This catheter undergoes a precise and predictable increase in cross-sectional diameter and decrease in stiffness when it is hydrated. In laboratory tests using crystalloid and whole blood, this change in cross-sectional diameter has been shown to allow a substantial increase in fluid flow through the catheter within 30 min of placement in saline at 37°C (1,2). Those in vitro tests showed that, with hydration, fluid flow through Streamline catheters increased to be approximately equal to flow through Teflon catheters two gauge sizes larger.

Before the present study, the in vitro findings had not been confirmed in vivo. Because vein anatomy, vascular resistance, and other in vivo effects may influence the fluid flow rate through IV lines, the present study was designed to test the fluid flow characteristics of these catheters in vivo. In this study, we compared the flow characteristics of 20-gauge Streamline catheters and 18-gauge CathlonIV (Critikon, Tampa, Fla.) Teflon catheters after IV placement in obstetric patients in a randomized, blinded fashion.

Methods

The protocol was approved by the Committee on Human Subjects in Medical Research of Stanford University Medical Center. Forty patients admitted to the Stanford University Labor and Delivery suite for nonemergent conditions were studied. Written informed consent was obtained from all subjects. All patients taking medication or with a history or symptoms of cardiac disease, respiratory disease, diabetes, or a need for fluid restriction were excluded from the study. Patients were randomly assigned to receive either a CathlonIV 18-gauge, 3.2-cm-long Teflon catheter or a Streamline 20-gauge, 3.2-cm-long catheter.

All catheters were placed in an arm or hand vein by an anesthesia resident or an anesthesiologist according to a standardized technique using 1% lidocaine for local anesthesia. After placement, a dressing was applied in a manner that obscured the identity of the catheter.

Five minutes after the catheter was placed through the skin, an independent investigator, blinded to the identity of the catheter, measured the amount of time required for the infusion of 50 mL of lactated Ringer's solution. After the initial measurement, IV fluid flow was adjusted by the obstetric nurse according to the patient's needs, usually at 125 mL/h. Sixty minutes after catheter placement, the flow measurement was repeated.

Fluid volume was measured using an IV burette (Abbott Laboratories, North Chicago, Ill.), and fluid was infused using a standard IV set (Venoset 78, Abbott Laboratories) with a 127-cm extension (No. 51K52L1122, American Pharmaseal Co., Valencia, Calif.). The fluid meniscus in the vented burette was maintained at 1 m above the catheter insertion site, which was held at the level of the heart. Each patient's arm and hand were kept resting on her abdomen in a neutral position during all measurements. Data were compared using paired and unpaired *t*-tests.

Results

Patient characteristics of age, weight, and estimated gestational age of the fetus did not differ between the groups. Data were obtained from 18 patients in the Streamline group and 20 patients in the CathlonIV

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Table 1. Flow Through Intravenous Catheters 5 min and 60 min After Placement

	5 min		60 min	
	Cathlon	Streamline	Cathlon	Streamline
Number of subjects	20	18	20	18
Catheter gauge size	18	20	18	20→18[a]
Mean flow, mL/min (±SD)	36.2 (±6.47)	32.8 (±6.79)	36.4 (±6.78)	40.87 (±8.55)[b]
Range of flow, mL/min	25–46.2	19.5–43.5	21.4–46.9	24–56.6
Mean percent change			+1	+24
Range of percent change			−24 to +28	+2 to +54

[a] Flow was found to increase in the Streamline catheters due to a change in catheter diameter after placement.

[b] $P < 0.001$ vs Streamline 5-min flows by paired *t*-tests.

group. Two patients in the Streamline group were withdrawn from the study at their request, in one case because of discomfort at the insertion site and another because of a probable vasovagal episode after placement.

Synthetic oxytocin (Pitocin, Parke-Davis, Morris Plains, N.J.) was used for induction or augmentation of labor in 12 patients with Streamline catheters and in 15 patients with CathlonIV catheters. In patients receiving oxytocin, dosage ranged from 2 to 6 mU/min at the 60-min measurement. No patient was receiving oxytocin at the time of the initial flow measurement. The total volume of fluid infused was unaffected by the use of oxytocin. No other drugs were administered to any patient.

The time required to infuse 50 mL was converted to fluid flow in milliliters per minute. Results are shown in Table 1. At the time of the initial measurement (5 min after placement of the catheters) fluid flow was not significantly different between the Streamline and CathlonIV groups. Fluid flow through Streamline catheters measured 60 min after placement increased an average of 24% over baseline values ($P < 0.001$ by paired *t*-tests), whereas mean flow through CathlonIV catheters did not change. At the time of the final, 60-min measurement, mean flow through Streamline 20-gauge catheters had increased but was not significantly different from that through CathlonIV 18-gauge catheters.

The use of oxytocin did not affect mean fluid flow rates in either group, nor did it affect the degree of increase in fluid flow rate in patients with Streamline catheters. Mean fluid flow rate was not affected by site of placement.

Discussion

Fluid flow rates through IV catheters are a function of catheter diameter and, to a lesser extent, length (3–5). Standard IV catheters are made of Teflon or other nonexpandable plastics in which the diameter is constant and fluid flow rate through the catheter does not increase with time. The Streamline catheter tested in the present study softens and expands upon exposure to saline or other aqueous fluid. This study confirms the in vitro finding that fluid flow through the Streamline catheter increases substantially with hydration, but, on the average, flow through a Teflon catheter does not change after placement.

A wide range of flows was observed with both catheter types. Flow through CathlonIV catheters increased in some patients, whereas it decreased in others; the mean change in flow was insignificant. Flow through Streamline catheters increased in all patients, but the range of increase was variable. The mean increase in flow observed in this study (24%) was less than the mean increase observed in laboratory investigations of the catheter (~100%) (1,2). This smaller increment in flow may be due to the 5 min elapsed time between catheter placement and the initial measurement, as catheter hydration and expansion is most rapid immediately after placement. Therefore, the initial measurement may have been elevated, thereby decreasing the observed percentage increase in flow.

The interpatient variations in flow may be due to differences in vein anatomy, vascular resistance, local vein response to the presence of the catheter, or other factors. Because of its softer consistency after hydration, the Streamline catheter may cause less endothelial damage, possibly resulting in less local venoconstriction. In another study, a catheter constructed of a polymer with softening characteristics similar to but much less pronounced than the Streamline has been shown to be associated with less frequent or severe thrombophlebitis than a Teflon catheter during IV use (6). Whereas the present study did not investigate the incidence of catheter-related complications, other preliminary studies have shown that infiltration, thrombophlebitis, and other complications occur significantly less often with a Streamline than with a standard Teflon catheter, and that the median time before the occurrence of such complications was much longer in patients using the Streamline (7,8). The problems leading to withdrawal of two patients from this study (pain at the insertion site and fainting) did not occur more frequently in Streamline patients than in control patients in a larger study (8). These beneficial effects have been ascribed to the softening of the catheter after placement, resulting in less mechanical trauma to vein endothelium.

Oxytocin was the only medication used during the study, and it was given to similar numbers of patients in both groups. Studies of the vasoactive properties of oxytocin in vitro found that it acts as a vasoconstrictor, with its threshold of effect found in concentrations in the range of 10^{-7} to 10^{-5} M (9). The doses used in the present study did not exceed 10^{-8} M at the catheter tip. This concentration was further diluted by blood flow through the vein, so the molar concentration of oxytocin at the vein endothelium was probably lower than 10^{-8} M. In human studies, the doses of oxytocin used do not have significant systemic hemodynamic effects (10). Therefore, it is unlikely that oxytocin use affected fluid flow through the vein.

Twenty-gauge Streamline IV catheters have previously been shown to flow at least as well as 18-gauge Critikon CathlonIV or Deseret (Becton Dickinson, Sandy, Utah) catheters in vitro. This study confirms in vivo the finding that 20-gauge Streamline IV catheters flow at least as well as 18-gauge Critikon CathlonIV catheters. This may offer a significant advantage in patients with difficult IV access, such as pediatric patients, obese patients, geriatric patients, IV drug abusers, and patients requiring long-term IV therapy. In such patients, usable veins often are limited in number and size, and the Streamline catheter may enable one to place a small catheter initially, when ultimately the fluid flow of a larger catheter may be needed.

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Induced Hypertension for Cerebral Aneurysm Surgery in a Patient With Carotid Occlusive Disease

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Key Words: ANESTHESIA, NEUROSURGICAL. SURGERY, NEUROLOGIC.

Elevations in systemic arterial pressure have been linked to the rupture of intracranial aneurysms (1). This association most likely reflects the relationship between systemic arterial pressure and the transmural pressure on the aneurysmal wall. Thus, blood pressure is carefully controlled in patients suffering subarachnoid hemorrhage and is frequently reduced intraoperatively with pharmacologic agents as an aneurysm is clipped (2–3). Although the judicious reduction of arterial pressure may benefit some patients by preventing aneurysmal rupture, such reductions could also prove injurious to patients with impaired cerebral perfusion (4). This report summarizes the course of a patient with an intracranial aneurysm and carotid occlusive disease who suffered a cerebral infarction after a iatrogenic reduction in arterial pressure in an intensive care unit. His neurologic symptoms partially resolved after the subsequent elevation of his arterial pressure; thus, arterial pressure was maintained at artificially high levels throughout his subsequent perioperative course.

Case Report

A 57-yr-old man presented to the emergency room of an outlying hospital with a chief complaint of severe headache of several hours duration and a past medical history significant only for untreated hypertension. On admission, his blood pressure was 220/100 mm Hg, his heart rate 80 beats/min, and his respiratory rate 20 breaths/min. Neurologic examination was unremarkable but a computed tomography scan demonstrated blood in the right Sylvian fissure and in the basal cisterns. Thus, a diagnosis of subarachnoid hemorrhage, Hunt–Hess grade I, was made.

The patient was admitted to an intensive care unit where his blood pressure was lowered to 120–140 mm Hg systolic with intravenous hydralazine (20 mg) and a labetalol infusion. Shortly thereafter he became disoriented and developed a new left hemiparesis. An arteriogram (performed the next day) showed an anterior communicating artery aneurysm and a total right internal carotid obstruction. No evidence of cerebral artery vasospasm was apparent. At this point, the decision was made to transfer the patient.

Upon arrival at our institution, all hypotensive agents were discontinued. Arterial and central venous catheters were placed, and the patient's blood pressure was elevated to approximately 170–190 mm Hg systolic (his baseline systolic blood pressure) with a phenylephrine infusion. His sensorium gradually cleared over the next 24 h, and the hemiplegia partially resolved. A follow-up computed tomography scan demonstrated a new right parietal cerebral infarction. The phenylephrine infusion was continued as required to maintain a systolic blood pressure of 170–190 mm Hg throughout his 11-day preoperative course at the Massachusetts General Hospital.

Fourteen days after hemorrhage, the patient arrived in the operating room (still receiving phenylephrine) for an elective clipping of the aneurysm. After preoxygenation, anesthesia was induced with sufentanil (2 μg/kg), thiopental (0.5 mg/kg), and pancuronium (0.1 mg/kg). Anesthetic maintenance was provided by nitrous oxide (70%), oxygen, and supplemental increments of sufentanil. Furosemide (20 mg) and mannitol (100 g) were administered intravenously to facilitate surgical exposure. Hyperventilation was not attempted during the procedure: the end-tidal carbon dioxide approximated 35 mm Hg (correlating with a $Paco_2$ of 38 mm Hg) throughout. The aneurysm was dissected and clipped uneventfully. Neuromuscular blockade was reversed with neostigmine and glycopyrolate (3.0 and 0.6 mg, respectively), and the nitrous oxide was discontinued.

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Phenylephrine was transiently discontinued as the patient emerged from anesthesia and was extubated. Neurologic examination in the operating room demonstrated a partial left hemiparesis unchanged from that found preoperatively.

Phenylephrine was reinstituted in the recovery room and was continued until the second postoperative day when the patient's baseline blood pressure returned to its previous hypertensive levels (i.e., to approximately 170 mm Hg systolic). His recovery was uneventful, and he was discharged to a rehabilitation hospital with a partial left hemiparesis.

Discussion

The perioperative management of a patient with both an intracranial aneurysm and carotid occlusive disease presents the anesthetist with distinct, and sometimes conflicting, challenges. On the one hand, blood pressure should be kept low to minimize the risk of recurrent subarachnoid hemorrhage (1). However, reductions in systemic arterial pressure are paralleled by reductions in cerebral perfusion pressure, thus placing patients with impaired cerebral perfusion (from either vasospasm or occlusive vascular disease) in jeopardy for ischemic brain injury. Our patient's early course illustrates this point: the blood pressure reduction was followed by a left hemiparesis, which partially resolved when his pressure was elevated with phenylephrine. Other explanations for this scenario seem less likely: cerebral vasospasm was not demonstrated at angiography, and the patient's neurologic abnormalities (i.e., disorientation and a left hemiparesis) were temporally related to the reduction in blood pressure, thus suggesting cerebral hypoperfusion as the probable etiology.

Cerebral ischemia and infarction represent major sources of morbidity and mortality for patients undergoing ligation of an intracranial aneurysm. Ischemia commonly results from cerebral artery vasospasm (5), but may also reflect concomitant carotid occlusive disease. The cerebral artery vasospasm is narrowing of the lumen in major cerebral arteries, which occurs for unclear reasons after subarachnoid hemorrhage. Elective perioperative elevation of blood pressure may be indicated in both disorders to increase the cerebral perfusion pressure and thus to reduce the potential for ischemic injury (6–8). Elevation of systemic arterial pressure has been advocated to improve cerebral perfusion in patients undergoing carotid endarterectomy (6) and has likewise been suggested to benefit patients with intracranial aneurysms and clinically significant vasospasm (7).

Several authors have advocated the early clipping of an intracranial aneurysm (i.e., within a few days after a low Hunt–Hess grade subarachnoid hemorrhage) to allow aggressive therapy with a combination of volume expansion and pharmacologically induced hypertension to improve cerebral perfusion, while minimizing the potential for rebleeding (9,10). The patient with carotid occlusive disease may similarly benefit from early ligation of an intracranial aneurysm, followed by volume expansion and induced hypertension as indicated.

A constellation of electrocardiographic changes (e.g., ST segment abnormalities, inverted T waves) may persist for several days after subarachnoid hemorrhage (11), thus complicating the diagnosis of myocardial ischemia. Although the relationship between such changes and myocardial injury is uncertain, electrocardiographic abnormalities in conjunction with subarachnoid hemorrhage are associated with a greatly increased mortality (12). If such electrocardiographic changes are present, or if the patient has a history of angina or congestive heart failure, pulmonary artery cannulation may be prudent before the initiation of hypertensive therapy. As myocardial infarction is a leading cause of morbidity and mortality in patients undergoing carotid endarterectomy (13), patients with intracranial aneurysms and carotid occlusive disease may also be at high risk.

Thus, contrary to common clinical practice, induced hypertension may prove useful in the perioperative management of the patient with an intracranial aneurysm at risk for ischemia from either vasospasm or carotid occlusive disease. Moreover, reductions in systemic arterial pressure in patients with cerebral aneurysms should be undertaken with caution, especially in patients at risk for concomitant vascular occlusive disease.

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Letters to the Editor

An Earpiece Modification to Facilitate Nasotracheal Intubation

Key Words: INTUBATION, TRACHEAL

To the Editor:

Recent concerns about safety and pathogen transmission have caused many anesthesiologists to modify their techniques in a variety of situations, including that of blind nasotracheal intubation. Dorsey and Jones (1), for example, promoted the use of a disposable heat/moisture exchanger to protect the operator from expelled secretions during blind nasotracheal intubation. Other authors have sought to distance the nasotracheal tube from the anesthetist's ear by placing earmold tubing loosely inside the endotracheal tube (2) or by attaching a miniature microphone to amplify breath sounds (3).

Reported here is a simple attachment to facilitate blind nasotracheal intubation, one that essentially eliminates direct respiratory contact with patients. This apparatus is made of readily available anesthetic gas analysis sampling parts and connects a standard oral-nasal endotracheal tube to the operator's earpiece (Figure 1). A straight elbow connector (PPG/Biomedical, SARA Straight Elbow, No. S215195001) attaches to the outer end of the endotracheal tube, and a male-male adaptor (Mallinckrodt, Male-Male Luer Lock Adaptor, No. 91229) allows the connection to the operator's earpiece (Figure 2). Optionally, the addition of an in-line filter (PPG/Biomedical, SARA Filter Kit, No. S215189001) further minimizes aerosol transmission. The entire disposable apparatus can be easily added to resuscitation kits, or carried in one's coat pocket for instant attachment to the anesthetist's ubiquitous earpiece.

By providing a more direct conduit for sound to the ear, this device allows intubation of patients with faint respiratory sounds or in noisy environments (e.g., emergency room). Negligible resistance is added to the patient's respiratory exchange. This device also eliminates the need for the anesthetist to bend over the patient's body, a position that might make him or her unable to view monitoring equipment or to maintain proper vigilance.

Having used this device recently for approximately 20 nasal intubations, I have had no difficulty in distinguishing the respiratory phases, or in assessing the tube's proximity to the larynx. Similar results have been obtained by three other anesthesiologists in my department. Breath sounds are somewhat higher pitched, with the amplitude dependent on the length of connecting tubing between the nasotracheal tube and the earpiece; therefore, short lengths are recommended to avoid excessive dampening of the sounds. It is also suggested that the apparatus be removed before the attachment of a breathing circuit, as potentially high-pressure gas could be insufflated into the operator's auditory canal.

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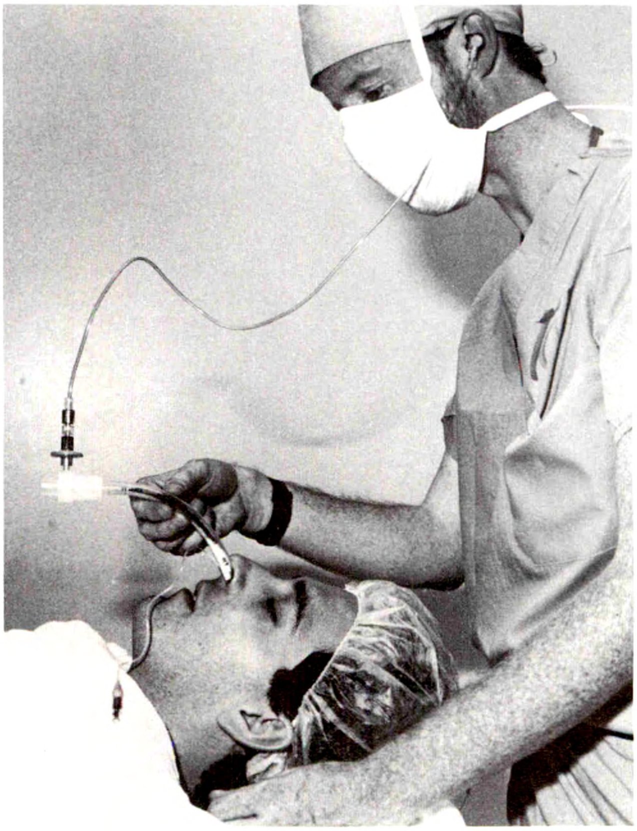

Figure 1. Earpiece modification attaches to nasotracheal tube to facilitate blind intubation, freeing operator from direct respiratory contact.

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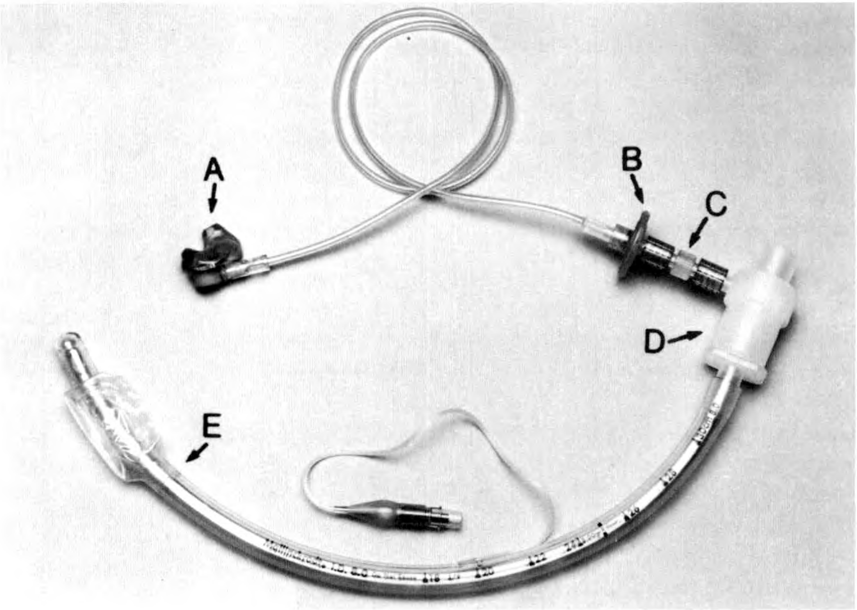

Figure 2. Earpiece (*A*) attaches to nasotracheal tube (*E*) through straight elbow connector (*D*) and male-male adaptor (C). Optional in-line filter (*B*) minimizes aerosol transmission.

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More About Jaundice and Oximetry

Key Words: MEASUREMENT TECHNIQUES, OXIMETRY. OXYGEN, MEASUREMENT.

To the Editor:

We read with great interest the paper by Beall and Moorthy about jaundice and oximetry (1). We would like to relate their findings to our recent clinical study (2). Two points are relevant to the use of oximetry in icteric patients.

First, hyperbilirubinemia induces a spectral error in cooximeters, leading them to overread carboxy- and methemoglobin levels and thus to underestimate the oxyhemoglobin level (3). We found different spectral errors among cooximeters. The IL 282 (Instrumentation Laboratory, Lexington, Mass.) (four wavelengths) was inaccurate when the total bilirubin level exceeded 10 mg/dL and the Corning Co-2500 (Corning, Medfield, Mass.) (seven wavelengths) when total bilirubin exceeded 30 mg/dL (3), whereas the OSM3 (Radiometer, Copenhagen, Denmark) (six wavelengths) seemed less affected (unpublished data). More-

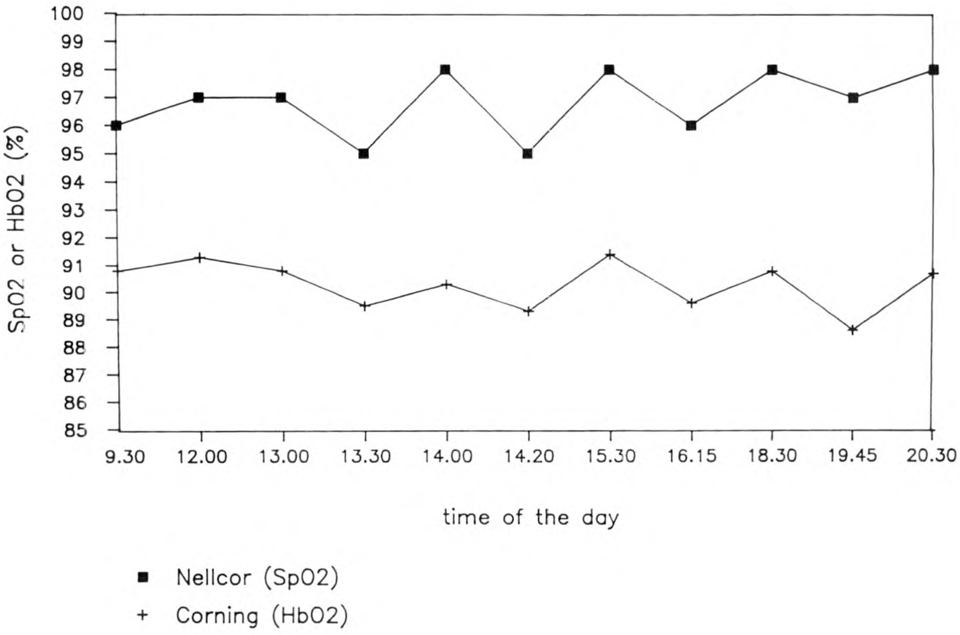

Figure 1. Twelve-hour trend of pulse oximetry readings (Sp_{O_2}) and oxyhemoglobin (Hb_{O_2}) (uncorrected for the spectral error due to bilirubin) in a very icteric patient (total bilirubin: 49 mg/dL; carboxyhemoglobin: 4.5% ± 0.3% [mean ± SD]).

over, this spectral error also varied with true oxyhemoglobin.

Second, carbon monoxide and bilirubin are both products of hemoglobin metabolism. Jaundice is therefore often associated with increased carboxyhemoglobin levels. Pulse oximeters are not directly influenced by high bilirubin levels (2) but overestimate oxyhemoglobin in the presence of carboxyhemoglobin (4).

In clinical practice, one should know which cooximeter is in use in the blood gas laboratory when interpreting the oxyhemoglobin, carboxyhemoglobin, and methemoglobin levels measured in severely icteric patients. On the other hand, pulse oximetry may yield fallaciously high readings in icteric patients, but its value in monitoring trends should not be affected by this systematic error (Figure 1).

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On Use of Priming With Vecuronium in a Patient With an Open Globe and a Full Stomach

Key Words: NEUROMUSCULAR RELAXANTS, VECURONIUM. INDUCTION, ANESTHESIA—rapid sequence.

To the Editor:

Berry and Merin (1) recently reported a case of vitreous herniation on induction of general anesthesia in a 90-kg patient presenting with a "full stomach" and "open globe." In the course of their anesthetic induction, 1 mg vecuronium (11 μg/kg) and 0.2 mg fentanyl were administered intravenously 5 min before the induction of general anesthesia with lidocaine and etomidate followed by 9 mg vecuronium for tracheal intubation. The authors mention in their discussion that "priming techniques have been documented to reduce the time to complete relaxation to approximately 60 sec with vecuronium" (1).

The study cited by the authors to document this claim (2) has, however, been criticized (3) for various reasons, including the fact that the study was not blinded and lacked a control group. We have shown (4) that the onset of conditions for tracheal intubation was not significantly different when vecuronium was given using the divided dose technique than it was when a similar group of patients were given the same total dose as a single bolus. Furthermore, a case of pulmonary aspiration has been described with the priming technique with vecuronium (5).

In view of the need for the rapid onset of profound paralysis for tracheal intubation in patients with an open globe and a full stomach, and in view of the uncertainty as to the efficacy of the priming technique, I recommend that either a single large bolus (0.25 mg/kg) of vecuronium (6) or succinylcholine (7) be used instead.

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In Response:

The letter by Sosis points out the advantages of high-dose vecuronium over a "priming" technique in possibly preventing pulmonary aspiration or uncomfortable decrements in inspiratory force before induction. We agree that priming doses of >0.012 mg/kg can be associated with these problems. As discussed on our case report (1), our objectives were to provide rapid intubating conditions, maintain hemodynamic stability, and preserve the contents of the open globe. In this patient, the observed myoclonus appeared immediately upon administration of etomidate (and after the intubating dose of vecuronium) and persisted for approximately 30 s. It is unclear whether the myoclonus disappeared spontaneously or because of the onset of neuromuscular blockade. We know of no studies addressing the dose and rapidity of effect of neuromuscular blocking agents on etomidate myoclonus, but adequate intubating conditions may not correlate with blockade of myoclonus. With the use of high-dose (0.25 mg/kg) vecuronium, the onset of neuromuscular block is no more rapid than with the "priming" techniques (2–4) and thus would not have diminished this patient's myoclonus. We maintain that, in combination with etomidate, the speed of onset of succinylcholine decreases the probability of prolonged etomidate myoclonus, and we would recommend it even in the patient with an open eye injury (5).

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Restless Legs During Recovery From Spinal Anesthesia

Key Words: ANESTHETIC TECHNIQUES, SPINAL.

To the Editor:

Restless leg syndrome has been described in a number of neurologic syndromes, including polio, vitamin deficiencies, diabetes, anemia, and after administration of phenothiazines (1). Lesions of the extrapyramidal and pyramidal tracts, the cerebellum, and lower motor neurons can also produce abnormal muscle activity. Myokymia has been described in patients with multiple sclerosis, central demyelinating diseases, tumors, and peripheral neuropathy (2). Typically, the patients describe an initial creeping sensation followed by motor activity that is both involuntary and distressful for the patient. Recently we encountered "restless legs" in a patient during recovery from spinal anesthesia. Abnormal muscle movement has been reported during spinal anesthesia (3). Clonic seizures and asymmetric myoclonic activity also have been reported after spinal anesthesia (4,5). The case that we describe is the first reported case of symmetric myoclonus during recovery from bupivacaine spinal anesthesia.

Our patient was a 69-yr-old man who underwent uneventful transurethral resection of the prostate. Spinal anesthesia with 12 mg bupivacaine was performed without difficulty. He was discharged from the recovery room when his blood pressure was normal and movement began to return to the feet. Ninety minutes after release from the recovery room the patient complained of uncontrolled movements of his legs. His primary complaint was that he had no sensation of position of his legs or control of the motor activity. Physical examination revealed choreoathetoid types of movement with partial flexion and adduction at the hip, extension of the knee, and partial plantar flexion occurring bilaterally with a clonic rhythm. The serum sodium level was normal. The patient received two intravenous doses of 5 mg diazepam, which reduced but did not eliminate the motor activity. After 45-60 min the movements subsided as sensation and proprioception returned. Because of the transient nature of our patient's problem we could not obtain an electromyogram.

As spinal anesthesia produces transient loss of lower motor neuron and sensory function, we postulate that the abnormal motor activity is a result of different rates of recovery of sensory and motor nerve fibers. Recovery of motor activity with incomplete recovery of sensation and proprioception would disrupt the normal proprioceptive feedback system.

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On Passage of Catheters Through Epidural Needles

Key Words: ANESTHETIC TECHNIQUES, EPIDURAL.

To the Editor:

I read with interest the article by Seitman and Shapiro (1) and commend them for emphasizing the need to check the contents of prepackaged epidural kits before use.

I should, however, take issue with their concern for passing the catheter through the needle in advance of the procedure. As this is carried out under direct observation, I believe that their fear of shearing the catheter is somewhat overstated (2). Surely it is better to ensure the potency of the epidural needle before insertion into the patient (3). Indeed, if we are looking for all the potential problems associated with defective epidural equipment, perhaps we should also test the patency and uniformity of the catheter before use (4).

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Intravenous Sedation During Hepatic Artery Chemotherapeutic Embolization

Key Words: LIVER, THERAPEUTIC EMBOLIZATION. EMBOLISM, HEPATIC—therapeutic.

To the Editor:

Recently, Loper et al. reported celiac plexus block for hepatic artery embolization to be superior to analgesia with intravenous (IV) morphine (1). We would like to report the use of IV sedation in patients receiving intrahepatic artery chemotherapy consisting of carmustine in lipiodol.

Lipiodol is a radiopaque oil used in hepatic artery chemotherapy (2,3) to aid drug binding to tumor sites and allow fluoroscopic visualization of the chemotherapeutic drug infusion. It is poorly soluble in blood, causing a transient embolization of the hepatic arteries. During infusion of carmustine in lipiodol, temporary but severe upper right quadrant pain develops that is related to hepatic ischemia caused by the lipiodol. The treatment is useful in patients who are poor surgical risks or in those with unresectable disease (1,4,5).

With institutional approval, and after obtaining individual informed consents, we studied eight adults having chemotherapy with hepatic arterial embolization who were managed during the procedure with IV sedation. The six men and two women had either an unresectable primary hepatoma or metastatic liver disease.

All patients were given 15–30 mL of sodium citrate orally before treatments. Monitoring included electrocardiogram, indirect blood pressure, pulse oximetry, and precordial stethoscope. All patients received 3–4 L/min of oxygen by nasal cannulae. During cannulation of the femoral artery mild sedation was provided with midazolam (1–3 mg in divided doses) and fentanyl (25–100 μg) intravenously. After arterial patency in the portal circulation had been established by angiogram, the level of sedation was increased with additional midazolam (1–4 mg) and fentanyl (50–100 μg). Just before infusion of the chemotherapeutic/embolizing agent, ketamine 10–20 mg was given intravenously. The infusions were completed in 10–15 min. With this technique, only one patient had recall of discomfort during the procedure, and this discomfort was only minimal.

The combination of midazolam, fentanyl, and ketamine intravenously provides adequate amnesia and analgesia for patients undergoing intrahepatic artery chemotherapeutic embolization. None of our patients developed oxygen desaturation during the procedure or required support of the airway. There were no episodes of emergence delirium. We report our experience as an alternative to celiac plexus block or high-dose IV narcotics to provide analgesia in patients in whom a temporary hepatic artery embolization is produced with an infusion of chemotherapeutic agents in lipiodol.

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ECG Changes With Electroconvulsive Therapy

Key Words: ANESTHESIA, ELECTROCONVULSIVE THERAPY. HEART, ELECTROCARDIOGRAPHY.

To the Editor:

Khoury and Benedetti (1) reported T-wave elevation during electroconvulsive therapy in several depressed but otherwise healthy patients, which they asserted was the first report of such observation. Graybar et al. (2) reported a similar case several years ago. Both sets of authors concluded that the T-wave changes were not associated with hyperkalemia or anesthetic technique and were more likely a product of sympathetic imbalance or transient intracranial damage.

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Erroneous Pulse Oximeter Data During CPR

Key Words: MEASUREMENT TECHNIQUES, PULSE OXIMETRY. COMPLICATIONS, CARDIAC ARREST—resuscitation.

To the Editor:

Pulse oximetry is an extremely useful monitor during the perioperative period and in a number of other clinical situations (1,2). Although pulse oximeter readings, particularly when using finger probes, can be erroneous during hypoperfusion and severe hypoxemia, pulse oximetry has been recommended for use during cardiopulmonary resuscitation (CPR) (3). We would like to emphasize that pulse oximetry cannot replace monitors such as electrocardiograms, the blood pressure cuff, and arterial pulse palpation during CPR.

The following acute events, one in the recovery room and one in the operating room, demonstrate our point. A 64-yr-old man with a history of myocardial infarction of indeterminate duration underwent an uneventful left thoracotomy and left upper lobectomy for carcinoma of the lung. Ninety minutes after surgery the patient complained of left-sided chest pain, abruptly sat up, and lost consciousness. At that time, when the electrocardiogram showed asystole, the pulse oximeter indicated 94% arterial oxygen saturation and a pulse rate of 72 beats/min. Clinically, asystole was suspected and immediate CPR was started. Although CPR was prolonged, it was, unfortunately, not successful. The second patient was a 58-yr-old man scheduled for resection of a lung carcinoma. After induction of anesthesia with thiopental and muscle relaxation with vecuronium the patient's trachea was intubated without difficulty. Soon after tracheal intubation ventilation became difficult because of a malfunctioning PEEP valve. Although the pulse oximeter registered a saturation of 92% and a pulse rate of 72 beats/min, the carotid pulse could not be palpated. A right tension pneumothorax was detected and a tube thoracostomy was performed. The patient had an uneventful recovery.

Most pulse oximeters require 8–10 s of asystole to indicate absence of the pulse and to initiate the alarm. Noise signals and movement of the patient's hands and fingers during CPR can, however, give erroneous indicators of hemoglobin saturation and pulse rate. The "signal alarm" should alert the anesthesiologist to check the electrocardiogram and pulse.

We evaluated two pulse oximeters with finger probes by using acute arterial occlusion with a blood pressure cuff. The results were similar for both pulse oximeters: movement of the fingers or hand with the finger probe in place during acute arterial occlusion produced false but physiologically acceptable readings and pulse wave patterns. The resultant misinterpretation can, under clinical conditions, lead both to incorrect judgment as to when CPR should be initiated and to the adequacy of CPR once it is initiated. We conclude that there is a finite lag time between cardiac arrest and the indication of arrest by the pulse oximeter. Furthermore, noise signals and limb movement during CPR produce spurious results. Pulse oximeter data must be interpreted in conjunction with the electrocardiographic and blood pressure data during CPR.

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One Hundred Thirty-Six Years of Ether Anesthesia

Key Words: HISTORY, ETHER. ANESTHETICS, VOLATILE—diethyl ether.

To the Editor:

It is well known in our specialty that the first recognized ether anesthesia was delivered at Massachusetts General Hospital in Boston in 1846. Someone may even remember that it was on October 16th of that year.

Less well documented and known is when the last ether anesthesia in the United States was administered. We believe and consider the ether anesthesia given to a patient in our institution on October 20, 1982, by Kenneth Lee, MD (staff) and Suzane Cooper, MD (resident) may well be the last one given in the United States.

This 1982 anesthetic was mentioned in the *Anesthesia History Association Newsletter* (1984;2(3/4):2); no one has written to us about any later ether anesthesia.

The anesthesia was given to an elderly gentleman who had recurrent cancer of his larynx-pharynx with a permanent tracheostomy. Anesthesia was induced with thiopental and then maintained with oxygen/nitrous oxide/ether. The procedure took 3 h and the patient tolerated the procedure well. He had had several previous procedures, some with ether.

We believe that this 1982 ether anesthesia may be of historical interest, and we would like to share this information with our colleagues. We are also looking forward to hearing from others who may have administered ether subsequent to October 20, 1982.

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A Method for Determining Depth of Unmarked Endotracheal Tubes Used in Laser Surgery

Key Words: EQUIPMENT, TUBES—endotracheal.

To the Editor:

The ability of a surgical laser to ignite a standard polyvinyl chloride endotracheal tube has been well documented, and this hazard has led to the development of a number of specialized endotracheal tubes for laser surgery in the airway (1–3). Depth markings are omitted from these protected endotracheal tubes because (a) the materials are difficult to mark and (b) the markings provide a site for increased energy absorption potentially leading to a hot spot or fire. The absence of depth markings on these tubes presents a problem in determining and accurately documenting depth of intubation as well as in recognizing and quantifying tube migration. During the evaluation of the 3.0-mm inside diameter Mallinckrodt Laserflex tube we developed a simple method for determining depth of endotracheal tube placement.

The depth of an endotracheal tube is normally specified by recording the distance from the tip of the tube as given by the scale printed on the tube at a point of reference on the patient (e.g., the teeth, gums, or lip). Referencing tube depth in this way does not give the actual location of the tip of the tube in relationship to the vocal cords or carina, but it does provide a consistent mechanism for determining relative tube placement. For a tube that is not marked, the depth of an endotracheal tube can be calculated by subtracting the distance from the reference point to the circuit connector from the distance from the tube tip to the circuit connector (length). This measurement process can be simplified by creating a depth guide that is the same length as the endotracheal tube, one that has a centimeter scale analogous to the markings on a standard endotracheal tube. Depth guides can be drawn individually and reproduced on a xerographic copier, or they can be made by cutting a paper measuring tape of the type used in the nursery (e.g., Baxter Catalog No. 30942) to the length of the endotracheal tube. After intubation the connector end of the depth guide is placed against the plastic connector and the depth guide is stretched along the endotracheal tube to the desired reference point. The distance from the tube tip to the reference point can then be read directly on the guide.

As the endotracheal tubes vary as to length, the use of a depth guide specific to one length of tube requires that a separate guide be made for each different tube. The use of a depth guide allows a simple and rapid determination of depth of intubation when tubes that lack depth markings are used, and it permits documentation of intubation depth in a manner consistent with current practice.

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The Cost of Continuous Infusions of Vecuronium in Critically Ill Patients

Key Words: NEUROMUSCULAR RELAXANTS, VECURONIUM. ECONOMICS, COSTS OF RELAXANTS.

To the Editor:

Coursin et al. (1) report two ventilator-dependent patients in whom continuous infusions of vecuronium were used to increase thoracic compliance and decrease oxygen consumption. They found that there was an increased requirement for vecuronium over the course of treatment (8–12 wk). Whether one concurs with the necessity for such muscle relaxation, and regardless of the considerable risks associated with such therapy, the cost of continuous vecuronium infusions is staggering.

At our institution the cost to the hospital of vecuronium is $13.21 per 10-mg vial. The charge to the patient is $27.82. In case 2 presented by Coursin and associates (1), the patient received 12 wk of vecuronium infusions increasing from 5 mg to 25 mg/h over the course of treatment. Let us assume this increase in vecuronium requirement was linear over the course of treatment. We may then estimate the total dose administered to be 30,240 mg. The charge to the patient at my institution would be $84,127.68 for the drug alone. This estimate ignores the pharmacy or nursing costs of preparing the infusions, administration sets, infusion pumps, intravenous maintenance, etc. Even if given at hospital cost, the bill would be $39,947.04.

Clinicians must be aware of the costs when they prescribe particular therapies. There are less expensive alternatives to vecuronium infusions, using older, less costly drugs with longer half-lives. Those aware of the high cost of this particular method of muscle relaxation may reconsider the use of vecuronium.

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Reference

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In Response:

We appreciate the salient points of Dr. Current's letter—in particular, that of the high cost of using a drug such as vecuronium for a protracted period of time. We also realize, as pointed out in his letter, that there may be significant additional costs such as pharmacy charges, cost of an infusion device, and the cost of additional personnel.

Our cases were, however, presented to point out an interesting phenomenon in two (now four) patients who received prolonged infusions of vecuronium. Our cases were not presented to recommend long-term infusions of vecuronium, but to describe the development of tachyphylaxis to infused vecuronium which developed over time in these patients. Our rationale for infusing vecuronium included (a) limited hemodynamic sequela; (b) relative ability to titrate to affect with the use of a nerve stimulator; (c) limited drug interaction; and (d) an attempt to maintain a relative constant depth of relaxation in patients at high risk from barotrauma or hemodynamic insufficiency.

We also realize that one must carefully weigh the risk benefit as well as the cost benefit when using any drug clinically. Finally, it is of interest that the cost to our patient for infusion of vecuronium was $20,000, well less than half the amount calculated by Dr. Current. In comparison, the cost of pancuronium bolus injection at 2 mg/h for the same time period would have been about $12,000. We find that the use of bolus injections in this clinical situation may be less satisfactory in avoiding swings in hemodynamics and in maintaining an adequate level of relaxation. We are also concerned about the potential for prolonged relaxation if muscle relaxants are administered on a timed basis.

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Book Reviews

Local Anesthesia and Regional Blockade

J. B. Löfström and U. Sjöstrand, eds. New York: Elsevier Science Publishing Co., Inc., 1988, 325 pp, $144.75.

If you do not have a sound knowledge of regional anesthesia, this book, which provides new facts and ideas essential for a fresh approach to the best possible use of local anesthetics and regional techniques, will be difficult to read. In the first two chapters, which discuss chemistry, pharmacology, and tissue uptake of local anesthetics and opioids, the need for considerable previous knowledge becomes evident. Carbonation and mixtures of local anesthetics, as well as addition of vasoconstrictors, macromolecules, and sustained release formulas for manipulation of the length of blockade are discussed. Lung uptake of endogenous substances and exogenous drugs such as local anesthetics is described very nicely. This buffer probably protects us from acute toxic reactions in connection with inadvertent intervascular injection of local anesthetics. Dr. Löfström provides a superb discussion of the effects of local anesthetics on circulation and respiration and clearly distinguishes effects on smooth muscle, arterial versus venous, splanchnic circulatory, and central nervous system. The discussion about respiration is brief, but includes the increased response to carbon dioxide caused by local anesthetics, and, more important, the decreased response to hypoxemia with combinations of analgetics and local anesthetics.

There is a good review of central nervous system and cardiovascular toxicity of local anesthetic agents, a review that is clear in its comparisons of different local anesthetic agents, and there is also a review of recent work on nerve toxicity of local anesthetics. Pathogenesis is divided into mechanical, toxic, and ischemic trauma. This part on peripheral nerves is very well written, but somewhat brief on spinal toxicity.

The anatomy of the lumbar epidural subarachnoid spaces is nicely described, with epiduroscopy and spinaloscopy. Anatomic explanations are given for many daily clinical problems. This part is short, clear, very new, and exciting.

Sensory and sympathetic block in connection with intra- and extradural analgesia is something we all thought that we understood fairly well. Dr. Bengtsson describes methods for estimation of spread and the factors of importance for spread and duration that cannot be controlled, such as age, weight, and height, as well as the controllable factors of volume, dose, gravity, choice of agent, vasoconstrictor, and injection technique. He also describes the resulting sympathetic blockade, which often is only partial and may even be considerably below the sensory level. Unfortunately, this review is somewhat confusing due to the high number of contradictory results presented. Additionally, the epidural portion is too brief.

Motor blockade and bladder function during spinal anesthesia are described. Bromage scale and more recently introduced quantitative isometric muscle strength measurements are compared. Here one finds a very good review of recent studies on motor block compared to sensory block in intradural analgesia. The description of regression compared to modified Bromage scale is interesting and clinically valuable. There are several good clinical comments and recommendations, but the epidural part is brief and not up-to-date, e.g., it is still discussing the use of 0.75% bupivacaine for extensive epidural blocks.

An extensive review of the effects of obstetric regional anesthesia on placental blood flow is given. Effects of local anesthetics and epidural anesthesia on coagulation, hemodynamics, fibrinolysis leading to decreased thrombosis, and pulmonary embolism are reviewed. Both these contributions are clear and clinically oriented. The description of the effects of general anesthesia with depression of the immune defense as opposed to regional anesthesia with a lack of immune depression is interesting, but its clinical importance is not yet fully understood.

The literature on spinal opiates is growing rapidly, and the pharmacokinetic aspects of this issue are discussed thoroughly. Clinical aspects are described clearly but somewhat superficially. The effect of neuroblockade on trauma and stress response is described in an informative but perhaps somewhat superficial chapter. The authors do make the important distinction between pain relief and block of stress response.

The psychological aspects of regional anesthesia are discussed by an experienced anesthesiologist, but there is a conspicuous lack of documentation of the different comments. Music of patients' own selection might not be the best; white sound or soft music is better according to some reports. The dose recommendation of fentanyl on page 276 must be a typo and should be 0.05–0.1 mg, not "0.5–0.1 mg."

There is a nice presentation of results regarding anes-

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thesia in wartime and civilian disasters, where there seems to be little room for regional anesthesia. Under less intense circumstances with good contact (verbal) with patients, regional anesthesia can be very valuable. Under this heading there is also a very well-written part about local anesthetics and its combination with hypnotics, acupuncture, sedation, and general anesthetics and its risks.

Dr. Covino gives a short review of new compounds and new, not yet clinically useful preparations such as methoxyflurane microdroplets, biotoxins, cyclizing agents, and tetraethylammonium derivatives. Although newer modifications such as bicarbonate addition and carbonation of local anesthetic agents can shorten the induction time and prolong the anesthetic, Covino finally turns to chemists, pharmacologists, and anesthesiologists with a request for new drugs.

In summary, if you belong to the target group of anesthesiologists and clinicians with interest in the field of regional anesthesia, you will enjoy reading this text. It is mostly of a very high quality, written mainly by a Scandinavian group of anesthesiologists who have fallen in love with regional anesthesia not because their patients have such a high pain threshold, but because of their long tradition of quality regional anesthesia and excellence in regional anesthetic research.

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Malignant Hyperthermia: Current Concepts

M. A. Nalda Felipe, S. Gottmann, H. J. Khambatta, eds.
Englewood, N.J.: Normed Verlag, 1989, 220 pp, $32.00.

It is incredible how much has been learned about malignant hyperthermia (MH) since the single case report of Denborough and Lovell in 1960. Perhaps the most important advance has been the rapid consciousness-raising that has occurred among anesthesiologists. Malignant hyperthermia is now the subject of numerous review articles, chapters in standard textbooks of anesthesia, and a popular refresher course topic. This increased awareness has helped to reduce mortality from >70% to <10%. In September 1988 a meeting took place in Barcelona to educate anesthesiologists in Spain about MH. This monograph contains the proceedings of that meeting.

Most of the chapters are reviews of the diagnosis and management of MH-susceptible patients. Although these chapters are comprehensive, they sometimes reflect the authors' biases on more controversial topics. For example, the role of emotional stress or nonanesthetic medications in triggering human MH is less clear-cut than described by Dr. Khambatta. Similarly, it is not accepted that signs of subclinical myopathy such as muscle cramps or strabismus are more prevalent in MH-susceptible patients. Rodrigo et al. discuss the anesthetic management of patients with myotonic dystrophy and state that MH prophylaxis is obligatory. However, many investigators believe that myotonic dystrophy is *not* associated with MH susceptibility and volatile anesthetic agents have been used safely in such patients for many years.

Each chapter contains several figures and/or tables, and most chapters are extensively referenced. However, this reviewer found several citation errors and was unable to locate many of the references. In addition typographical errors abound and distract the reader from the author's message.

"Malignant Hyperthermia—The Clinical Differential Diagnosis" by Jantzen et al. is a novel chapter that describes the diagnostic possibilities of a case of MH and emphasizes that most of the signs of acute MH are nonspecific. Therefore, a high index of suspicion is required. The authors suggest that metabolic monitoring with capnography, thermometry, and mixed venous oximetry can assist in the diagnosis of MH.

Another chapter that reviews the reports of deaths due to MH despite dantrolene therapy is a keen, well-written discussion that, unfortunately, comes to a simple conclusion: that dantrolene must be given in adequate doses as early as possible to avoid death. The authors rightly emphasize the importance in treating acute MH of (a) discontinuing triggering agents; (b) *hyper*ventilation with 100% oxygen; and (c) intravenous dantrolene. Their review showed that an overemphasis on symptomatic therapy, particularly cooling measures, most likely led to several avoidable deaths.

There is one clear omission in the book. Although a chapter appears on the North American halothane caffeine contracture test, there is no detailed description of the protocol of the European MH Group.

Several chapters in this book may interest those who study MH, and who are familiar with its literature. However, this book cannot be recommended as a review of MH for the novice for it has not undergone peer review and some topics are presented as less controversial than they truly are.

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Anesthesia and New Surgical Procedures: Anesthesiology Clinics of North America

A. S. Wheeler, ed. Philadelphia: W.B. Saunders, 1989,
258 pp, $69.00 per year.

This issue of the *Clinics* series takes on the challenge of familiarizing anesthesiologists and nurses with the pathophysiologic, technical, and anesthetic considerations of new surgical procedures brought about by recent advances in medical technology. The book contains 12 chapters written by different authors with extensive experience in these new anesthetic procedures.

The strongest chapters cover liver and pancreatic transplantation, with excellent reviews of underlying pathophysiology, concise explanations of surgical and technical aspects, and thorough coverage of special anesthetic considerations for transplant recipients. Although transplantation of the liver or pancreas is currently performed only at selected major medical centers, these chapters provide a reasonable starting point for any anesthesiologist interested in these procedures and supply extensive references for further study.

The chapter on anesthetic and monitoring problems associated with the widespread use of magnetic resonance imaging is needed and welcome. A well-written chapter on anterior spinal surgery includes coverage of endobronchial intubation, the physiology of one-lung ventilation, and the use of somatosensory evoked potentials to monitor certain spinal cord functions. Unfortunately, there is no mention in this chapter of the "wake-up" test, the most commonly used test to assess motor function. The chapter on replantation of extremities presents a strong argument for regional anesthesia but does not offer any comparison of the outcome of regional versus general anesthesia studies.

Several chapters present good reviews of disease processes and associated anesthetic concerns without presenting new information. For instance, any practitioner who is prepared to anesthetize a patient with Parkinson's disease and who is familiar with a stereotaxic frame (perhaps, for brain biopsy) should already be familiar with the special anesthetic concerns for an adrenal-caudate transplant. The same observation can be made for the chapters dealing with temporomandibular joint arthroscopy and in vitro fertilization.

This multiauthored text includes areas of repetition. For example, laser surgery of the airway is discussed in two chapters. Although a few errors in editing and printing were noted, an excellent index appears in the back. In summary, this book discusses new anesthetic challenges not covered in the major anesthesiology textbooks.

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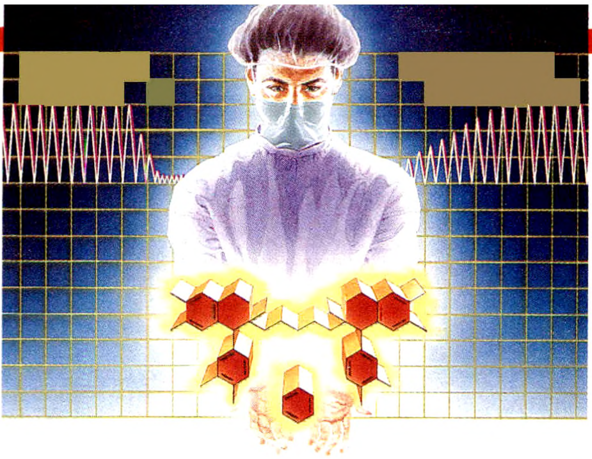
Issues in surgical muscular relaxation



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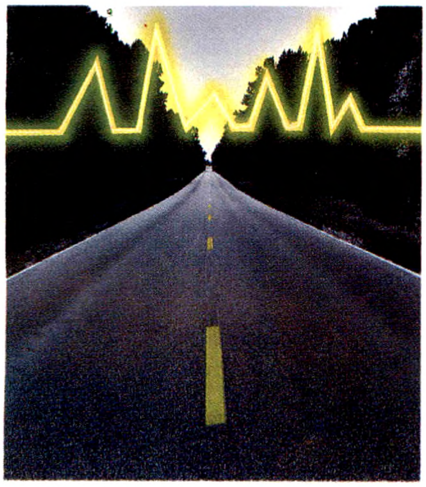

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Brief Summary

This drug should be used only by adequately trained individuals familiar with its actions, characteristics, and hazards.

INDICATIONS AND USAGE: Tracrium is indicated, as an adjunct to general anesthesia, to facilitate endotracheal intubation and to provide skeletal muscle relaxation during surgery or mechanical ventilation.

CONTRAINDICATIONS: Tracrium is contraindicated in patients known to have a hypersensitivity to it.

WARNINGS: TRACRIUM SHOULD BE USED ONLY BY THOSE SKILLED IN AIRWAY MANAGEMENT AND RESPIRATORY SUPPORT. EQUIPMENT AND PERSONNEL MUST BE IMMEDIATELY AVAILABLE FOR ENDOTRACHEAL INTUBATION AND SUPPORT OF VENTILATION, INCLUDING ADMINISTRATION OF POSITIVE PRESSURE OXYGEN. ADEQUACY OF RESPIRATION MUST BE ASSURED THROUGH ASSISTED OR CONTROLLED VENTILATION. ANTICHOLINESTERASE REVERSAL AGENTS SHOULD BE IMMEDIATELY AVAILABLE.

DO NOT GIVE TRACRIUM BY INTRAMUSCULAR ADMINISTRATION.

Tracrium has no known effect on consciousness, pain threshold, or cerebration. It should be used only with adequate anesthesia.

Tracrium Injection, which has an acid pH, should not be mixed with alkaline solutions (e.g., barbiturate solutions) in the same syringe or administered simultaneously during intravenous infusion through the same needle. Depending on the resultant pH of such mixtures, Tracrium may be inactivated and a free acid may be precipitated.

Tracrium Injection 10 mL multiple dose vials contain benzyl alcohol. Benzyl alcohol has been associated with an increased incidence of neurological and other complications in newborn infants which are sometimes fatal. Tracrium Injection 5 mL ampuls and 5 mL single use vials do not contain benzyl alcohol.

PRECAUTIONS:

General: Although Tracrium is a less potent histamine releaser than d-tubocurarine or metocurine, the possibility of substantial histamine release in sensitive individuals must be considered. Special caution should be exercised in administering Tracrium to patients in whom substantial histamine release would be especially hazardous (e.g., patients with clinically significant cardiovascular disease) and in patients with any history (e.g., severe anaphylactoid reactions or asthma) suggesting a greater risk of histamine release. In these patients, the recommended initial Tracrium dose is lower (0.3 to 0.4 mg/kg) than for other patients and should be administered slowly or in divided doses over one minute.

Since Tracrium has no clinically significant effects on heart rate in the recommended dosage range, it will not counteract the bradycardia produced by many anesthetic agents or vagal stimulation. As a result, bradycardia during anesthesia may be more common with Tracrium than with other muscle relaxants.

Tracrium may have profound effects in patients with myasthenia gravis, Eaton-Lambert syndrome, or other neuromuscular diseases in which potentiation of nondepolarizing agents has been noted. The use of a peripheral nerve stimulator is especially important for assessing neuromuscular blockade in these patients. Similar precautions should be taken in patients with severe electrolyte disorders or carcinomatosis.

Multiple factors in anesthesia practice are suspected of triggering malignant hyperthermia (MH), a potentially fatal hypermetabolic state of skeletal muscle. Halogenated anesthetic agents and succinylcholine are recognized as the principal pharmacologic triggering agents in MH-susceptible patients; however, since MH can develop in the absence of established triggering agents, the clinician should be prepared to recognize and treat MH in any patient scheduled for general anesthesia. Reports of MH have been rare in cases in which Tracrium has been used. In studies of MH-susceptible animals (swine) and in a clinical study of MH-susceptible patients, Tracrium did not trigger this syndrome.

Resistance to nondepolarizing neuromuscular blocking agents may develop in burn patients. Increased doses of nondepolarizing muscle relaxants may be required in burn patients and are dependent on the time elapsed since the burn injury and the size of the burn.

The safety of Tracrium has not been established in patients with bronchial asthma.

Long-Term Use in Intensive Care Unit (ICU): Tracrium has been used to facilitate mechanical ventilation in ICU patients. When there is a need for long-term mechanical ventilation, the benefits to risk ratio of neuromuscular blockade must be considered.

There is only limited information on the efficacy and safety of Tracrium administered by long-term (days to weeks) intravenous infusion to facilitate mechanical ventilation in intensive care facilities. For Tracrium, as with other neuromuscular blocking agents used in intensive care facilities, available evidence suggests that there is wide interpatient variability in dosage requirements and that these requirements may change with time. Limited data suggest that Tracrium infusion requirements may increase with prolonged administration in the ICU.

As with other neuromuscular blocking agents, little information is available on the plasma levels or clinical consequences of atracurium metabolites following long-term (days to weeks) infusion of Tracrium in the intensive care unit setting. One metabolite of atracurium, laudanosine, when administered alone to laboratory animals, has been associated with cerebral excitatory effects. Physiological effects of laudanosine in humans have not been demonstrated. The effects of hemodialysis, hemoperfusion and hemofiltration on plasma levels of atracurium and its metabolites are unknown.

Drug Interactions: Drugs which may enhance neuromuscular blocking action of Tracrium include: enflurane; isoflurane; halothane; certain antibiotics, especially the aminoglycosides and polymyxins; lithium; magnesium salts; procainamide; and quinidine.

If other muscle relaxants are used during the same procedure, the possibility of a synergistic or antagonist effect should be considered.

The prior administration of succinylcholine does not enhance the duration, but quickens the onset and may increase the depth, of neuromuscular blockade induced by Tracrium. Tracrium should not be administered until a patient has recovered from succinylcholine-induced neuromuscular blockade.

Carcinogenesis, Mutagenesis, Impairment of Fertility: A positive response was observed in the mouse lymphoma assay under conditions which killed over 80% of the treated cells. A far weaker response was observed in the presence of metabolic activation at concentrations which also killed over 80% of the treated cells.

Pregnancy: ***Teratogenic Effects:*** Pregnancy Category C. Tracrium has been shown to be potentially teratogenic in rabbits, when given in doses up to approximately one-half the human dose. There are no adequate and well-controlled studies in pregnant women. Tracrium should be used during pregnancy only if the potential benefit justifies the potential risk to the fetus.

Labor and Delivery: It is not known whether muscle relaxants administered during vaginal delivery have immediate or delayed adverse effects on the fetus or increase the likelihood that resuscitation of the newborn will be necessary. The possibility that forceps delivery will be necessary may increase.

Tracrium (0.3 mg/kg) has been administered to 26 pregnant women during delivery by cesarean section. No harmful effects were attributable to Tracrium in any of the newborn infants, although small amounts of Tracrium were shown to cross the placental barrier. The possibility of respiratory depression in the newborn infant should always be considered following cesarean section during which a neuromuscular blocking agent has been administered. In patients receiving magnesium sulfate, the reversal of neuromuscular blockade may be unsatisfactory and Tracrium dose should be lowered as indicated.

Nursing Mothers: It is not known whether this drug is excreted in human milk. Caution should be exercised when Tracrium is administered to a nursing woman.

Pediatric Use: Safety and effectiveness in children below the age of 1 month have not been established.

ADVERSE REACTIONS:

Observed in Controlled Clinical Studies: Tracrium produced few adverse reactions during extensive clinical trials. Most were suggestive of histamine release (see Precautions Section). The overall incidence rate for clinically important adverse reactions was 7/875 or 0.8%.

Most adverse reactions were of little clinical significance unless they were associated with significant hemodynamic changes. Substantial vital sign changes greater than or equal to 30% observed in 530 patients, without cardiovascular disease, were as follows: In those patients given the recommended initial dosage range of 0.31 to 0.50 mg/kg of Tracrium, mean arterial pressure increased in 2.8% and decreased in 2.1% of patients while the heart rate increased in 2.8% of these patients. At doses of $\geq$ 0.60 mg/kg, 14.3% of the studied patients had a decrease in mean arterial pressure while 4.8% had an increase in heart rate. At doses $\leq$ 0.30 mg/kg, mean arterial pressure increased in 1.9% and decreased in 1.1% of patients, while heart rate increased in 1.6% and decreased in 0.8% of these patients.

Observed in Clinical Practice: Based on clinical experience in the U.S. and the United Kingdom of approximately 3 million patients given Tracrium the following adverse reactions are among the most frequently reported: *General:* allergic reactions (anaphylactic or anaphylactoid) which, in rare instances, were severe (e.g., cardiac arrest); *Musculoskeletal:* inadequate, prolonged block; *Cardiovascular:* hypotension, vasodilatation (flushing), tachycardia, bradycardia; *Respiratory:* dyspnea, bronchospasm, laryngospasm; *Integumentary:* rash, urticaria, injection site reaction.

STORAGE: Tracrium Injection should be refrigerated at 2° to 8°C (36° to 46°F) to preserve potency. DO NOT FREEZE. *Upon removal from refrigeration to room temperature storage conditions (25°C/77°F), use Tracrium Injection within 14 days even if rerefrigerated.*

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[1] Payne J: Atracurium. *Semin Anesth* 1984;3:303-311.

[2] Basta S, Ali H, Savarese J: Clinical pharmacology of atracurium besylate (BW 33A): A new nondepolarizing muscle relaxant. *Anesth Analg* 1982;61:723-729.

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273 K/D

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316 L/E

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345A/F

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343A/C

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341A/C

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339A/C

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334A/C

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337A/F

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350A/C

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354B/G

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359B/G

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346AC

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344C/H

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361C

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362C

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363CD

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From time to time, faculty positions are available for both clinical anesthesiologists and research staff. These appointments are for immediate and future placement. Please respond prior to May 31, 1990 by sending your CV to Paul G. Barash, MD, Chairman, Department of Anesthesiology, Yale University School of Medicine, PO Box 3333, New Haven, CT 06510. Yale is an affirmative action employer and provides equal opportunities for employment to all applicants.

364C

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365C/E

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366CD

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369C/F

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372CD

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374C

THE UNIVERSITY OF MICHIGAN, CHAIR, DEPARTMENT OF ANESTHESIOLOGY

The University of Michigan Medical School is seeking an academic leader to direct the teaching, research, and patient care programs of its Department of Anesthesiology. Qualifications include an MD degree and board certification in anesthesiology, national stature as an investigator, clinical excellence, commitment to medical and graduate medical education, and significant experience in a leadership role in an academic medical center. The position includes a tenured faculty appointment. Please respond by March 16, 1990 to Edward McGuire, MD, Chair, Anesthesiology Search Task Force, c/o Ms. Jeanne Kin, Staff Assistant to the Dean, The University of Michigan Medical School, M7325A Medical Science Building I, Ann Arbor, MI 48109-0624. The University of Michigan is a nondiscriminatory/Affirmative Action Employer.

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376C/E

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378C/E

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385C

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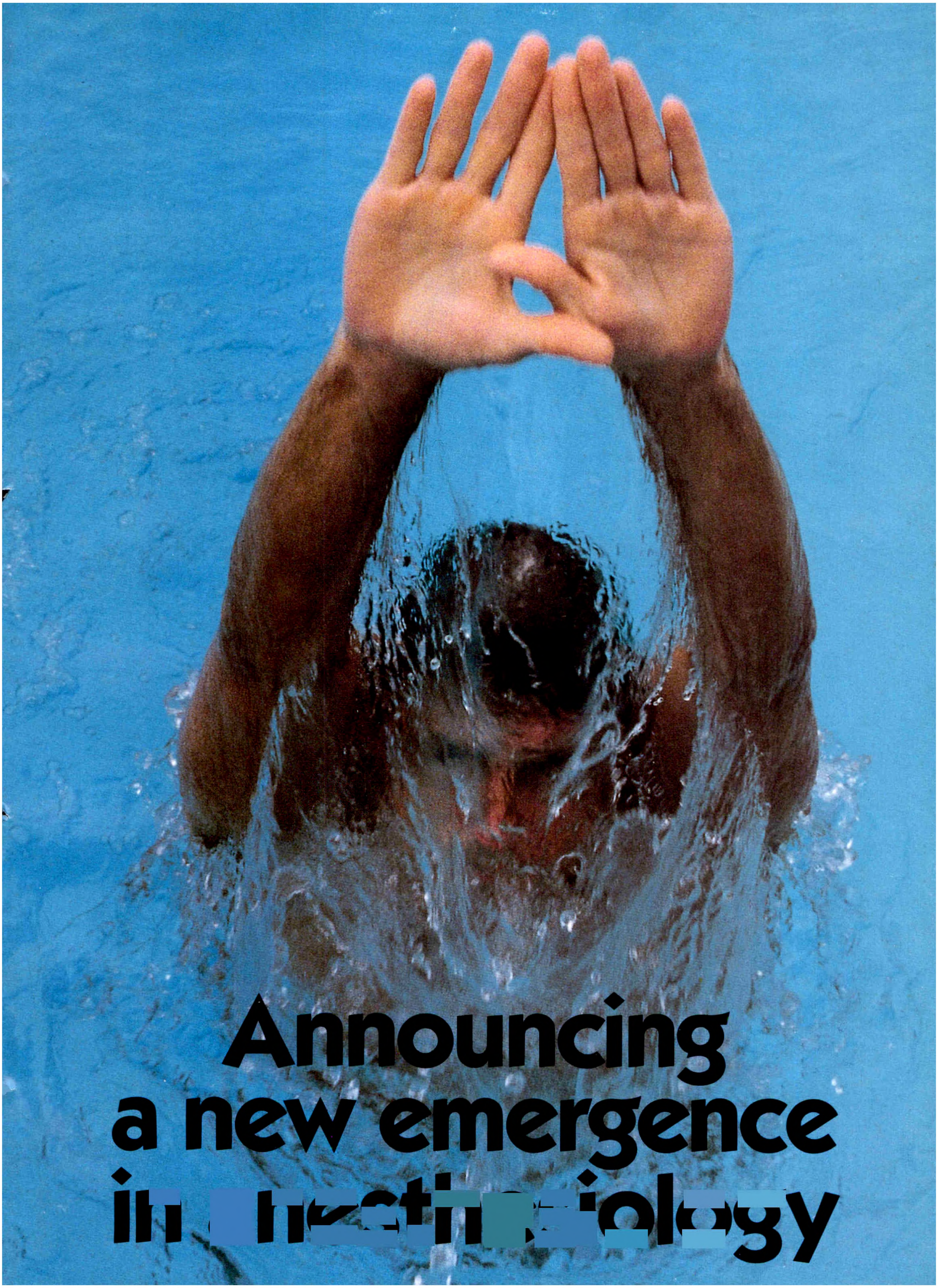
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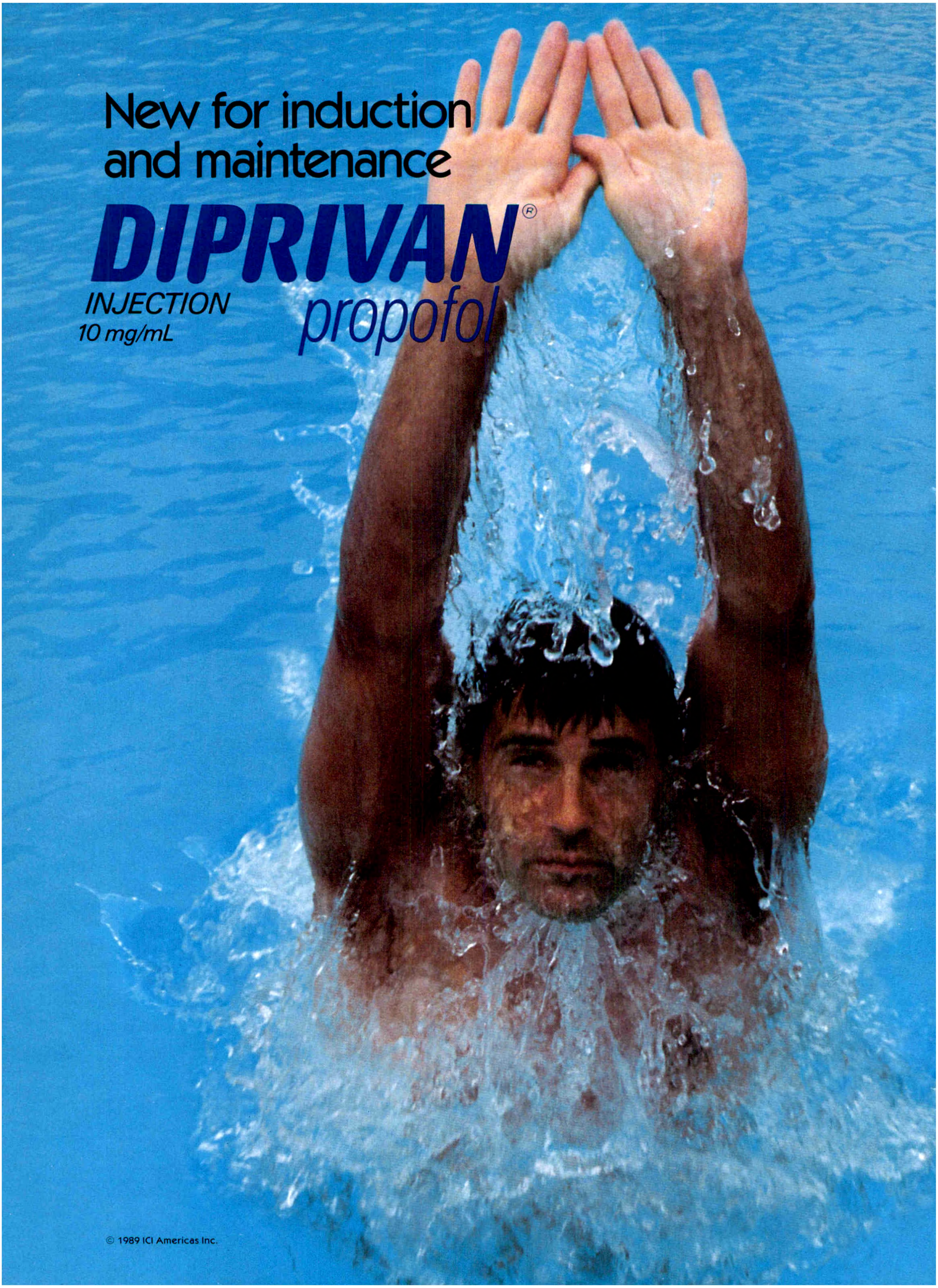

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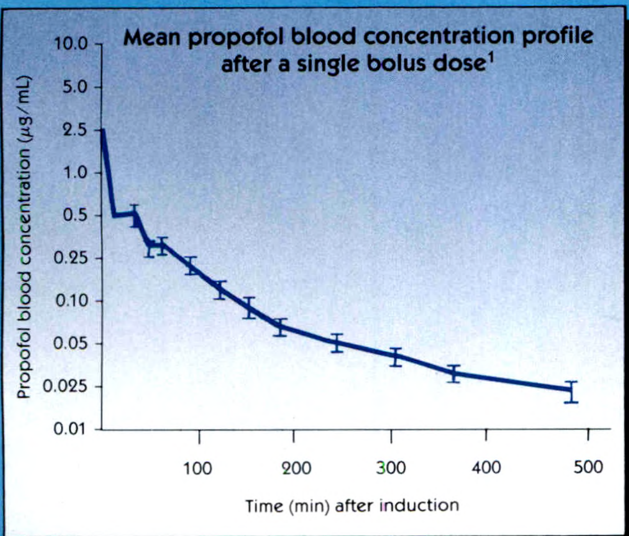

—adapted from Cockshott, p 46[1]

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5-10 times faster **than barbiturates**

	Clearance rate (L/min)†
DIPRIVAN	1.6–3.4
thiopental[3]	.11–.30
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—adapted from Way and Trevor, p 803[3]

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Fully oriented	5.5	9.4
Able to tolerate fluids	61*	130
Able to stand unassisted	68	87
Able to walk unassisted	70	96
Able to void	102*	173
"Ready" for home	138*	206

*Statistically significant ($P < 0.05$).
Measurements taken from time of discontinuation of all maintenance anesthesia.

With less of the nausea and vomiting associated with other anesthetic agents—up to 24 hours postop

Superior recovery

Improved speed and quality of recovery compared with thiopental/isoflurane:

- more rapid time to extubation[5]
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- patients able to tolerate fluids faster[2,4]

Earlier discharge from PARR*

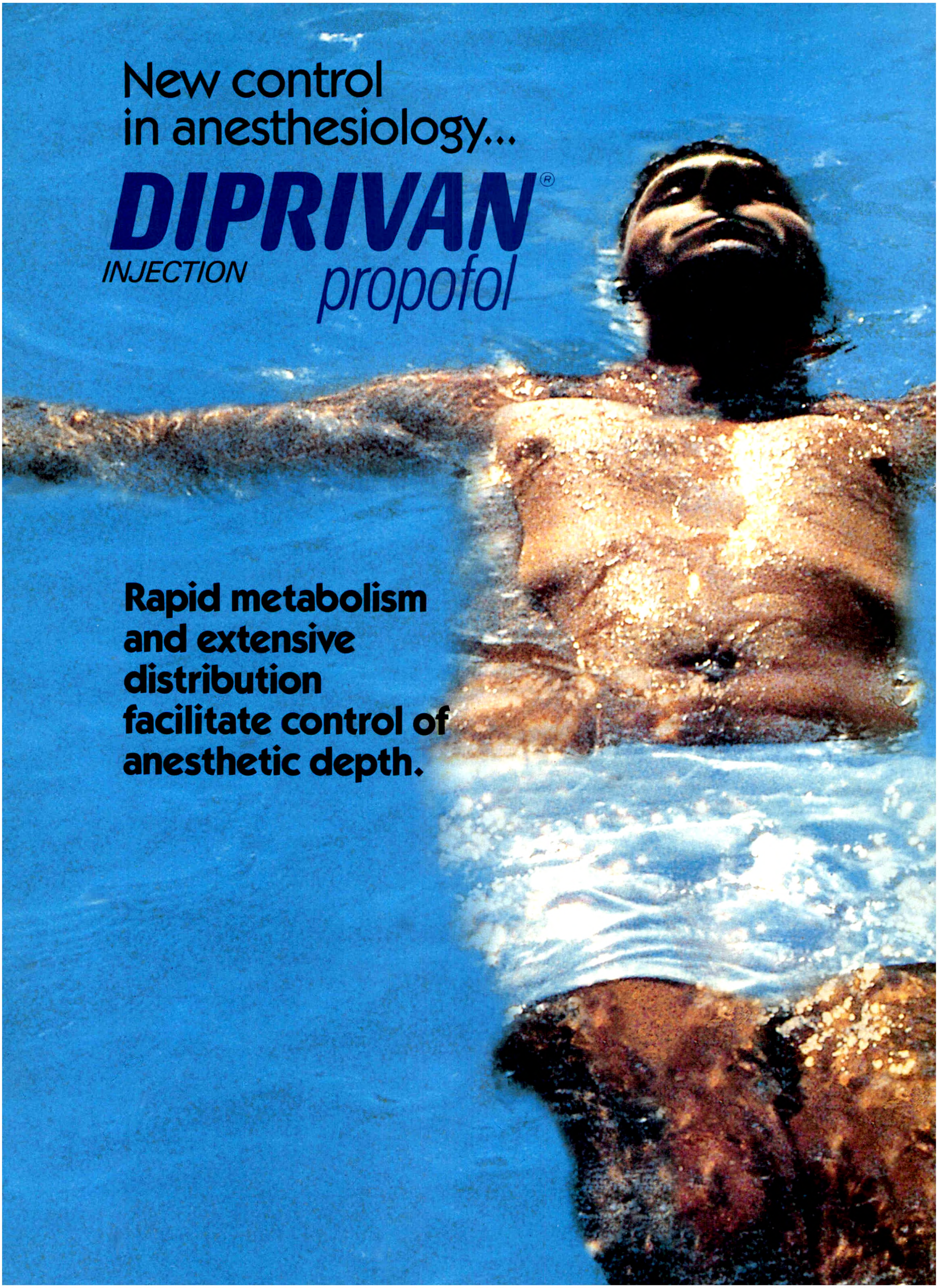
- more efficient utilization of OR/PARR facilities[9]
- increased nursing efficiency[9]
- rapid return to routine self-care activities

As part of a balanced anesthetic technique, DIPRIVAN is a cost-effective alternative to standard induction agents and volatile maintenance agents.

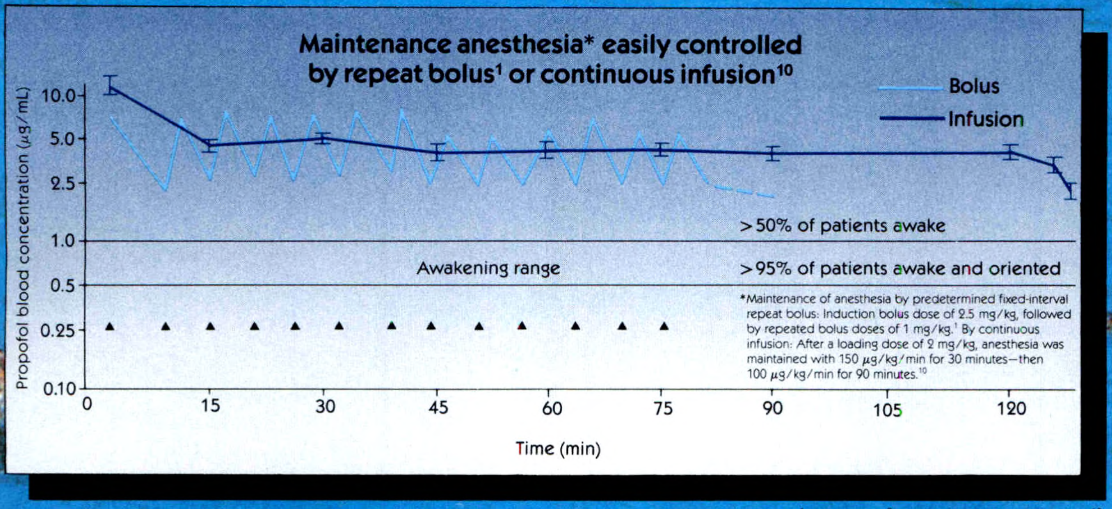
DIPRIVAN®
INJECTION
propofol

*An adequate period of evaluation of the awakened patient is indicated to ensure satisfactory recovery from general anesthesia.

Please see last pages of this advertisement for full prescribing information.


New control in anesthesiology...
DIPRIVAN®
INJECTION
propofol
Rapid metabolism and extensive distribution facilitate control of anesthetic depth.

Maintenance of anesthesia: easily controlled



Maintenance anesthesia* easily controlled by repeat bolus[1] or continuous infusion[10]

*Maintenance of anesthesia by predetermined fixed-interval repeat bolus: Induction bolus dose of 2.5 mg/kg, followed by repeated bolus doses of 1 mg/kg.[1] By continuous infusion: After a loading dose of 2 mg/kg, anesthesia was maintained with 150 µg/kg/min for 30 minutes—then 100 µg/kg/min for 90 minutes.[10]

—adapted from Cockshott, p 48,[1] White, p 9,[8] and Herregods et al, p 364[10]

No reported awareness during maintenance with DIPRIVAN

Overall quality of maintenance anesthesia superior to thiopental/isoflurane.[11]

Assessment of maintenance*[11]

	Excellent	Good	Poor
DIPRIVAN (n = 50)	**58%**	**30%**	**12%**
Thiopental + isoflurane (n = 50)	36%	32%	32%

*Statistically significant differences between all treatment groups ($P < 0.05$, Mantel-Haenszel Test)—as measured by the percent variation from baseline in hemodynamic parameters.

—adapted from Weingarten and Youngberg, data on file[11]

When used with N_2O/O_2 for maintenance, supplementation with IV analgesic agents is generally required; muscle relaxants may also be required.

DIPRIVAN®
INJECTION
propofol

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New assurance in anesthesiology...

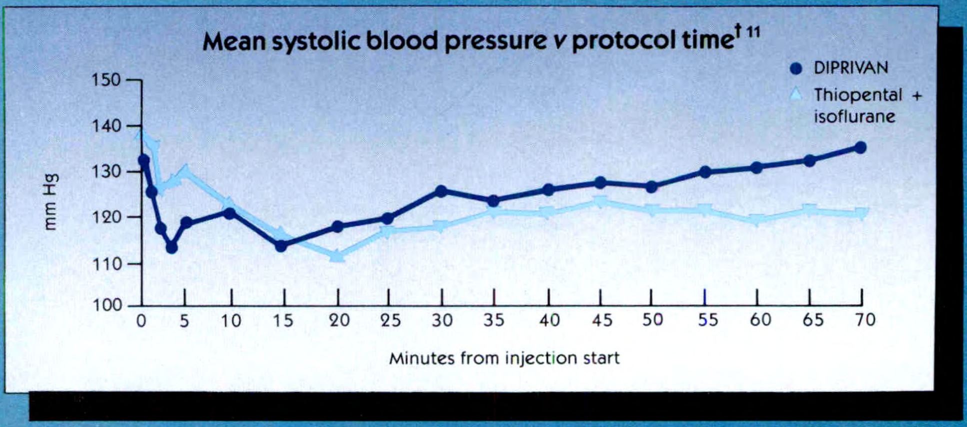
DIPRIVAN®

INJECTION *propofol*

Worldwide experience in over 7,000,000 patients

Hemodynamic and respiratory effects are dose-dependent

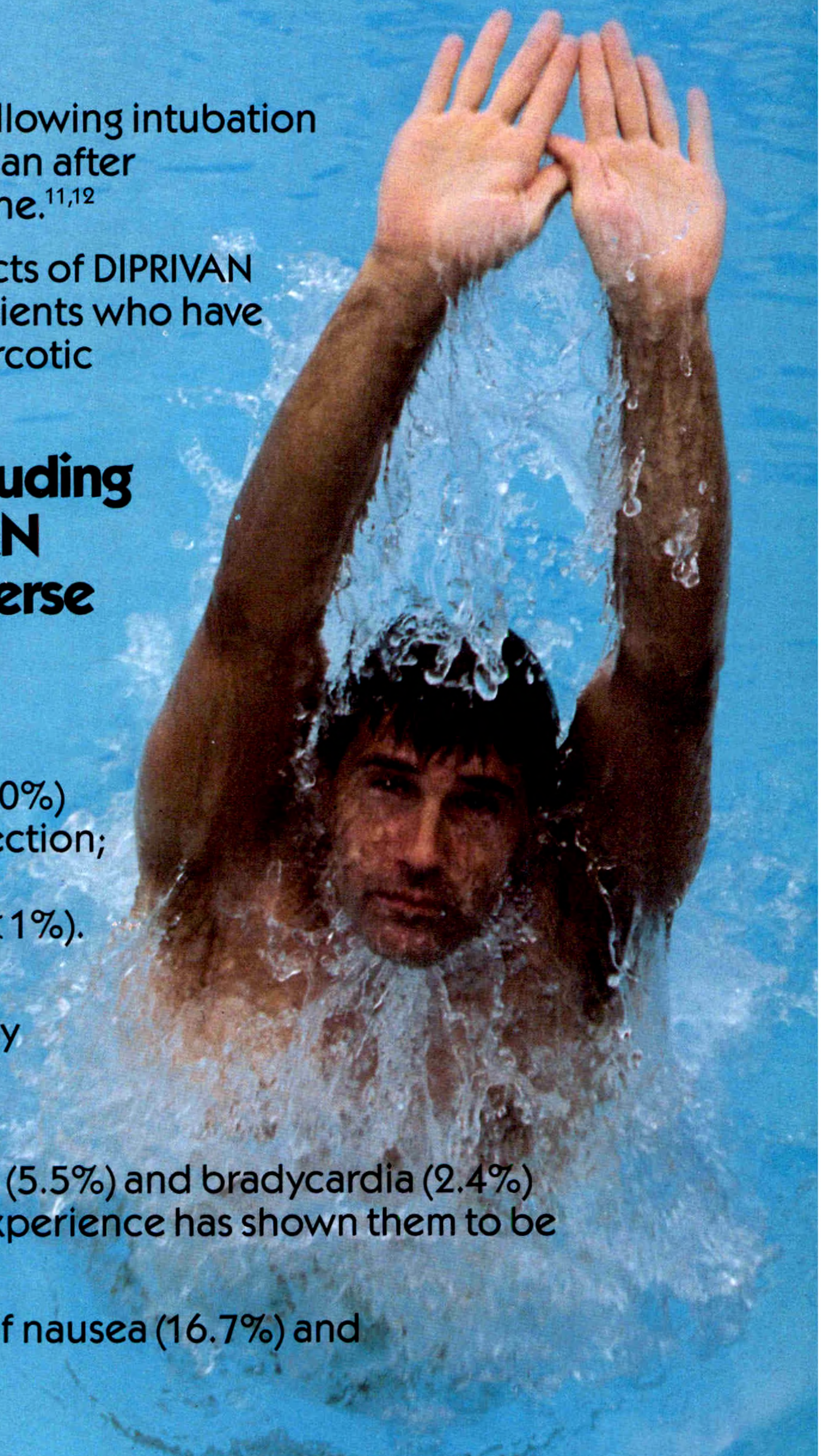
- Hemodynamic effects during induction were generally more pronounced than with traditional IV induction agents.
- Blood pressure predictably decreased on induction (sometimes >30%) but was within acceptable ranges for healthy individuals.*



—adapted from Weingarten and Youngberg, data on file[11]

[†] Induction bolus dose: Patients received either DIPRIVAN 2.5 mg/kg or thiopental 5.0 mg/kg. DIPRIVAN patients were then maintained with repeated injections of 25% of the original induction dose supplemented with 60% to 70% nitrous oxide in oxygen. Thiopental/isoflurane patients were maintained with 0.2% to 2.0% isoflurane supplemented with 60% to 70% nitrous oxide in oxygen.[11]

* Elderly, debilitated, and/or hypovolemic patients, and those rated ASA III/IV, may have more profound adverse cardiovascular responses.



- Increase in heart rate following intubation was less pronounced than after thiopental with isoflurane.[11,12]
- The cardiovascular effects of DIPRIVAN may be increased in patients who have received sedative or narcotic premedications.*

In clinical trials including over 1500 DIPRIVAN patients, most adverse events were mild and transient

- Transient local pain (≥10%) may occur during IV injection; venous sequelae have rarely been reported (<1%).
- Apnea often occurs on induction (43%) and may persist for more than 60 seconds.
- Significant hypotension (5.5%) and bradycardia (2.4%) have been reported†; experience has shown them to be clinically manageable.
- Low overall incidence of nausea (16.7%) and vomiting (9.1%).

*Induction dose requirements may be reduced.

†Sufficient to require intervention.

DIPRIVAN®
INJECTION *propofol*

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New versatility
in anesthesiology...

DIPRIVAN®
INJECTION *propofol*

**For a wide variety of procedures...
outpatient and inpatient**

- Gynecologic
- Orthopedic
- ENT
- Urologic
- Dermatologic
- General surgery
- Ophthalmic
- Diagnostic

DIPRIVAN should be administered only by persons trained in the administration of general anesthesia. **Facilities for maintenance of a patent airway, artificial ventilation, and oxygen enrichment and circulatory resuscitation must be immediately available.**

DIPRIVAN should be used with caution in elderly, debilitated, and/or hypovolemic patients, and those rated ASA Class III or IV.

DIPRIVAN is not recommended at this time for use in pediatric patients, nursing mothers, patients with increased intracranial pressure or impaired cerebral circulation, and in obstetrics, including cesarean section deliveries.

- DIPRIVAN can be combined with other commonly used agents in anesthesia.
- Also eliminates concerns about operating room/ recovery room pollution associated with volatile agents.

Please see last pages of this advertisement for full prescribing information.

For induction
and maintenance...

DIPRIVAN®

INJECTION
10 mg/mL
propofol

The new IV anesthetic agent with a unique pharmacokinetic profile

- for rapid, predictable onset of anesthesia
- for smooth induction with minimal excitation
- for easily controlled maintenance of anesthesia
- for rapid, clearheaded awakening—with a low incidence of nausea and vomiting

Extensive worldwide experience

in a wide variety of surgical procedures—outpatient and inpatient

As part of a balanced anesthetic technique, DIPRIVAN is a cost-effective alternative to standard induction agents and volatile maintenance agents.

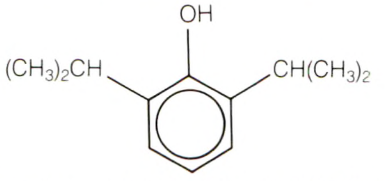
REFERENCES: **1.** Cockshott ID. Propofol ('Diprivan') pharmacokinetics and metabolism: an overview. *Postgrad Med J.* 1985;61(suppl 3):45-50. **2.** Korttila K, Faure E, Apfelbaum J, Östman P, Roizen M. Less nausea and vomiting after propofol than after enflurane or isoflurane anesthesia. *Anesthesiology.* 1988;69(3A):A578. Abstract. **3.** Way WL, Trevor AJ. Pharmacology of intravenous nonnarcotic anesthetics. In: Miller RD, ed. *Anesthesia.* 2nd ed. New York, NY: Churchill Livingstone; 1986:803. **4.** Korttila K, Faure E, Apfelbaum J, Ekdawi M, Prunskis J, Roizen M. Recovery from propofol versus thiopental-isoflurane in patients undergoing outpatient anesthesia. *Anesthesiology.* 1988;69(3A):A564. Abstract. **5.** Cork RC, Scipione P, Vonesh MJ, Magarelli JL, Pittman RG. Propofol infusion vs. thiopental/isoflurane for outpatient anesthesia. *Anesthesiology.* 1988;69(3A):A563. Abstract. **6.** Vinik HR. Exponential infusion of Diprivan (propofol): a randomized comparison with methohexital and thiopental/isoflurane for induction and maintenance of anesthesia. *Semin Anesth.* 1988;7(suppl 1):94-98. **7.** Weingarten M. Diprivan (propofol) for induction and maintenance of general anesthesia: experience from two clinical studies. *Semin Anesth.* 1988;7(suppl 1):85-90. **8.** White PF. Propofol: pharmacokinetics and pharmacodynamics. *Semin Anesth.* 1988;7(suppl 1):4-20. **9.** Marais ML, Maher MW, Wetchler BV, Korttila K, Apfelbaum JL. Reduced demands on recovery room resources with propofol (Diprivan) compared to thiopental-isoflurane. *Anesthesiol Rev.* 1989;16(1):29-40. **10.** Herregods L, Rolly G, Versichelen L, Rosseel MT. Propofol combined with nitrous oxide-oxygen for induction and maintenance of anaesthesia. *Anaesthesia.* 1987;42:360-365. **11.** Weingarten M, Youngberg JA. A multicenter, comparative study of Diprivan for the induction and maintenance of anesthesia by repeat bolus administration versus thiopental sodium for induction followed by inhalation anesthesia for maintenance. Data on file, Stuart Pharmaceuticals, Wilmington, Delaware. **12.** Gold MI, Sacks DJ, Grosnoff DB, Herrington CA. Comparison of propofol with thiopental and isoflurane for induction and maintenance of general anesthesia. *J Clin Anesth.* 1989;1:272-276.

DIPRIVAN®

INJECTION propofol

EMULSION FOR IV ADMINISTRATION

DESCRIPTION: DIPRIVAN® (propofol) Injection is a sterile, nonpyrogenic emulsion containing 10 mg/mL of propofol suitable for intravenous administration. Propofol is chemically described as 2,6-Diisopropylphenol and has a molecular weight of 178.27. The empirical and structural formulas are:



$C_{12}H_{18}O$

Propofol is very slightly soluble in water and, thus, is formulated in a white, oil-in-water emulsion. The emulsion is isotonic and has a pH of 7.0-8.5. In addition to the active component, propofol, the formulation also contains soybean oil (100 mg/mL), glycerol (22.5 mg/mL) and egg lecithin (12 mg/mL); with sodium hydroxide to adjust pH.

CLINICAL PHARMACOLOGY: DIPRIVAN Injection is an intravenous hypnotic agent for use in the induction and maintenance of anesthesia. The pharmacokinetic profile of DIPRIVAN Injection can be characterized as follows: After a single rapid IV bolus dose, two distribution phases are seen, a rapid phase with a half-life of 1.8 to 8.3 min and a slower phase of 34 to 64 min. These distribution phases are associated with the movement of DIPRIVAN from highly perfused tissues (vessel-rich tissues) to less well-perfused tissues. The terminal elimination half-life of DIPRIVAN ranges from 300 to 700 min. With prolonged administration of DIPRIVAN Injection, the terminal elimination half-life may become extended beyond 700 min. DIPRIVAN has a high metabolic clearance that ranges from 1.6 L/min to 3.4 L/min in healthy 70 kg patients. This metabolic clearance exceeds estimates of hepatic blood flow, suggesting possible extrahepatic metabolism. DIPRIVAN has a large steady state distribution volume that ranges from 150 to 1,000 liters in healthy 70 kg patients. The long terminal elimination half-life of DIPRIVAN is due to the large steady state distribution volume which is presumed to be due to extensive drug partitioning into tissues.

The termination of anesthetic drug effects of DIPRIVAN after a single IV bolus or a maintenance infusion is due to extensive redistribution from the CNS to other tissues and high metabolic clearance both of which will decrease blood concentrations. Recovery from anesthesia is rapid. Following induction (2.0 to 2.5 mg/kg DIPRIVAN Injection) and maintenance (0.1 to 0.2 mg/kg/min) of anesthesia for periods up to two hours, the majority of patients are generally awake, responsive to verbal commands, and oriented within 8 minutes. Recovery from the effects of DIPRIVAN Injection occurs due to metabolism and distribution during the first two exponents of the decay curve and is not dependent on the terminal elimination half-life. A study in six subjects showed approximately 70% of the administered radiolabeled DIPRIVAN Injection dose was recovered in the urine in the first 24 hours and approximately 90% of the dose was recovered in the urine within five days. DIPRIVAN is chiefly metabolized by conjugation in the liver to inactive metabolites which are excreted by the kidney. A glucuronide conjugation metabolite accounted for about 50% of the administered dose. The exact metabolic fate of DIPRIVAN and the sites of possible "extrahepatic" metabolism have not been identified.

The phamacokinetics of DIPRIVAN Injection do not appear to be altered by gender, chronic hepatic cirrhosis or chronic renal failure. The effects of acute hepatic or renal failure on the pharmacokinetics of DIPRIVAN have not been studied. With increasing age the clearance of DIPRIVAN decreases from a mean ± S.D. of 1.8 ± 0.4 L/min in young (18-35 years) patients to a value of 1.4 ± 0.4 L/min in elderly (65-80 years) patients. When given by an infusion for up to two hours, the pharmacokinetics of DIPRIVAN appear to be independent of dose (0.05-0.15 mg/kg/min) and similar to IV bolus pharmacokinetics. The steady state propofol blood concentrations are proportional to the rate of administration.

Other drugs that cause CNS depression (hypnotics/sedatives, inhalational anesthetics and narcotics) can increase the CNS depression induced by DIPRIVAN. Morphine premedication (0.15 mg/kg) with N_2O 67% has been shown to decrease the necessary DIPRIVAN Injection maintenance infusion rate and therapeutic blood concentrations, when compared to a nonnarcotic (lorazepam) premedication. An alfentanil infusion rate of 50 μg/kg/h has been shown to replace the anesthetic effects of N_2O 67% and morphine premedication.

Intravenous injection of a therapeutic dose of DIPRIVAN Injection produces hypnosis rapidly and smoothly with minimal excitation, usually within 40 seconds from the start of an injection (one arm-brain circulation time). As with other rapidly acting intravenous anesthetic agents, the half-time of blood-brain equilibration is approximately 1 to 3 minutes, and this accounts for the rapid induction of anesthesia.

Propofol blood concentrations required for maintenance of anesthesia have not been completely characterized.

When nitrous oxide, oxygen, and propofol are used for maintenance of general anesthesia, supplementation with analgesic agents (eg, narcotics) is generally required; neuromuscular blocking agents may also be required. (See DOSAGE AND ADMINISTRATION.)

The hemodynamic effects of DIPRIVAN Injection during induction of anesthesia vary. If spontaneous ventilation is maintained, the major cardiovascular effects are arterial hypotension (sometimes greater than a 30% decrease) with little or no change in heart rate and no appreciable decrease in cardiac output. If ventilation is assisted or controlled (positive pressure ventilation), the degree and incidence of decrease in cardiac output are accentuated. Addition of a potent opioid (eg, fentanyl) when used as a premedicant further decreases cardiac output.

If anesthesia is continued by infusion of DIPRIVAN Injection, endotracheal intubation and surgical stimulation may return arterial pressure towards normal. However, cardiac output may remain depressed. Comparative clinical studies have shown that the hemodynamic effects of DIPRIVAN during induction are generally more pronounced than with traditional IV induction agents.

Insufficient data are available regarding the cardiovascular effects of DIPRIVAN Injection when used for induction and/or maintenance of anesthesia in elderly, hypovolemic, hypotensive, debilitated patients, patients with severe cardiac disease (ejection fraction < 50%) or other ASA III/IV patients. However, limited information suggests that these patients may have more profound adverse cardiovascular responses. It is recommended that if DIPRIVAN Injection is used in these patients, a lower induction dose and a slower maintenance rate of administration of the drug be used. (See DOSAGE AND ADMINISTRATION.)

Clinical and preclinical studies suggest that DIPRIVAN Injection is rarely associated with elevation of plasma histamine levels and does not cause signs of histamine release.

Induction of anesthesia with DIPRIVAN Injection is frequently associated with apnea. In 1573 patients who received DIPRIVAN Injection (2.0 to 2.5 mg/kg), apnea lasted 0-30 seconds in 7% of patients, 30-60 seconds in 24% of patients, and more than 60 seconds in 12% of patients. During maintenance DIPRIVAN Injection (0.1 to 0.2 mg/kg/min) causes a decrease in ventilation usually associated with an increase in carbon dioxide tension which may be marked depending upon the rate of administration and other concurrent medications (eg, narcotics, sedatives, etc.).

Clinical studies in humans and studies in animals show that DIPRIVAN Injection does not suppress the adrenal response to ACTH.

Preliminary findings in patients with normal intraocular pressure indicate that DIPRIVAN Injection anesthesia produces a decrease in intraocular pressure which may be associated with a concomitant decrease in systemic vascular resistance.

Animal studies and limited experience in susceptible patients have not indicated any propensity of DIPRIVAN Injection to induce malignant hyperthermia.

INDICATIONS AND USAGE: DIPRIVAN Injection is an IV anesthetic agent that can be used for both induction and/or maintenance of anesthesia as part of a balanced anesthetic technique for inpatient and outpatient surgery.

DIPRIVAN Injection is not recommended for obstetrics, including cesarean section deliveries, because there are insufficient data to support its safety to the fetus. (See PRECAUTIONS.)

DIPRIVAN Injection is not recommended for use in nursing mothers because DIPRIVAN Injection has been reported to be excreted in human milk and the effects of oral absorption of small amounts of propofol are not known. (See PRECAUTIONS.)

DIPRIVAN Injection is not recommended for use in pediatric patients because safety and effectiveness have not been established. (See PRECAUTIONS.)

DIPRIVAN Injection is not recommended for use at this time in patients with increased intracranial pressure or impaired cerebral circulation because DIPRIVAN Injection may cause substantial decreases in mean arterial pressure, and consequently, substantial decreases in cerebral perfusion pressure. (See PRECAUTIONS.)

CONTRAINDICATIONS: When general anesthesia is contraindicated or in patients with a known hypersensitivity to DIPRIVAN Injection or its components.

WARNINGS: DIPRIVAN Injection should be administered only by persons trained in the administration of general anesthesia. **Facilities for maintenance of a patent airway, artificial ventilation, and oxygen enrichment and circulatory resuscitation must be immediately available.**

DIPRIVAN Injection should not be coadministered through the same IV catheter with blood or plasma because compatibility has not been established. In vitro tests have shown that aggregates of the globular component of the emulsion vehicle have occurred with blood/plasma/serum from humans and animals. The clinical significance is not known.

PRECAUTIONS: General: A lower induction dose and a slower maintenance rate of administration should be used in elderly, debilitated and/or patients with circulatory disorders, and those rated ASA III or IV. (See DOSAGE AND ADMINISTRATION.) Patients should be continuously monitored for early signs of significant hypotension and/or bradycardia. Treatment may include increasing the rate of intravenous fluid, elevation of lower extremities, use of pressor agents, or administration of atropine. Apnea often occurs during induction and may persist for more than 60 seconds. Ventilatory support may be required. Because DIPRIVAN Injection is an emulsion, caution should be exercised in patients with disorders of lipid metabolism such as primary hyperlipoproteinemia, diabetic hyperlipemia, and pancreatitis.

Since DIPRIVAN Injection is never used alone, an adequate period of evaluation of the awakened patient is indicated to ensure satisfactory recovery from general anesthesia prior to discharge of the patient from the recovery room or to home.

Transient local pain may occur during intravenous injection, which may be reduced by prior injection of IV lidocaine (1.0 mL of a 1% solution). Venous sequelae (phlebitis or thrombosis) have been reported rarely (< 1%). In two well-controlled clinical studies using dedicated intravenous catheters, no instances of venous sequelae were reported up to 14 days following induction. Pain can be minimized if the larger veins of the forearm or antecubital fossa are used. Accidental clinical extravasation and intentional injection into subcutaneous or perivascular tissues of animals caused minimal tissue reaction. Intra-arterial injection in animals did not induce local tissue effects. One accidental intra-arterial injection has been reported in a patient, and other than pain, there were no major sequelae.

Perioperative myoclonia, rarely including opisthotonus, has occurred in a temporal relationship in cases in which DIPRIVAN Injection has been administered.

Rarely, a clinical syndrome which may include bronchospasm and erythema accompanied by hypotension has occurred shortly after the administration of DIPRIVAN Injection, although the use of other drugs in most instances makes the relationship to DIPRIVAN Injection unclear.

Drug Interactions: As DIPRIVAN Injection has no vagolytic activity, premedication has usually included anticholinergic agents (eg, atropine or glycopyrrolate) to modify potential increases in vagal tone due to concomitant agents (eg, succinylcholine) or surgical stimuli.

The induction dose requirements of DIPRIVAN Injection may be reduced in patients with intramuscular or intravenous premedication, particularly with narcotics (eg, morphine, meperidine, and fentanyl) and combinations of narcotics and sedatives (eg, benzodiazepines, barbiturates, chloral hydrate, droperidol, etc). These agents may increase the anesthetic effects of DIPRIVAN Injection and may also result in more pronounced decreases in systolic, diastolic, and mean arterial pressures and cardiac output.

During maintenance of anesthesia, the rate of DIPRIVAN Injection administration should be adjusted according to the desired level of anesthesia and may be reduced in the presence of supplemental analgesic agents (eg, nitrous oxide or opioids). The concurrent administration of potent inhalational agents (eg, isoflurane, enflurane, and halothane) during maintenance with DIPRIVAN Injection has not been extensively evaluated. These inhalational agents can also be expected to increase the anesthetic and cardiorespiratory effects of DIPRIVAN Injection.

DIPRIVAN Injection does not cause a clinically significant change in onset, intensity or duration of action of the commonly used neuromuscular blocking agents (eg, succinylcholine and nondepolarizing muscle relaxants).

No significant adverse interactions with commonly used premedications or drugs used during anesthesia (including a range of muscle relaxants, inhalational agents, analgesic agents, and local anesthetic agents) have been observed.

Carcinogenesis, Mutagenesis, Impairment of Fertility: Animal carcinogenicity studies have not been performed with propofol.

In vitro and in vivo animal tests failed to show any potential for mutagenicity by propofol. Tests for mutagenicity included the Ames (using *Salmonella* sp) mutation test, gene mutation/gene conversion using *Saccharomyces cerevisiae*, in vitro cytogenetic studies in Chinese hamsters and a mouse micronucleus test.

Studies in female rats at intravenous doses up to 15 mg/kg/day (6 times the maximum recommended human induction dose) for 2 weeks before pregnancy to day 7 of gestation did not show impaired fertility. Male fertility in rats was not affected in a dominant lethal study at intravenous doses up to 15 mg/kg/day for 5 days.

Pregnancy Category B: Reproduction studies have been performed in rats and rabbits at intravenous doses of 15 mg/kg/day (6 times the recommended human induction dose) and have revealed no evidence of impaired fertility or harm to the fetus due to propofol. Propofol, however, has been shown to cause maternal deaths in rats and rabbits and decreased pup survival during the lactating period in dams treated with 15 mg/kg/day (or 6 times the recommended human induction dose). The pharmacological activity (anesthesia) of the drug on the mother is probably responsible for the adverse effects seen in the offspring. There are, however, no adequate and well-controlled studies in pregnant women. Because animal reproduction studies are not always predictive of human responses, this drug should be used during pregnancy only if clearly needed.

Labor and Delivery: DIPRIVAN Injection is not recommended for obstetrics, including cesarean section deliveries, because there are insufficient data to support its safety to the fetus.

Nursing Mothers: DIPRIVAN Injection is not recommended for use in nursing mothers because DIPRIVAN has been reported to be excreted in human milk and the effects of oral absorption of small amounts of propofol are not known.

Pediatric Use: DIPRIVAN Injection is not recommended for use in pediatric patients because safety and effectiveness have not been established.

Neurosurgical Anesthesia: Studies to date indicate that DIPRIVAN Injection decreases cerebral blood flow, cerebral metabolic oxygen consumption, and intracranial pressure, and increases cerebrovascular resistance. DIPRIVAN Injection does not seem to affect cerebrovascular reactivity to changes in arterial carbon dioxide tension. Despite these findings, DIPRIVAN Injection is not recommended for use at this time in patients with increased intracranial pressure or impaired cerebral circulation because DIPRIVAN Injection may cause substantial decreases in mean arterial pressure, and consequently, substantial decreases in cerebral perfusion pressure. Further studies are needed to substantiate what happens to intracranial pressure following DIPRIVAN Injection when decreases in mean arterial and cerebral perfusion pressures are prevented by appropriate measures.

ADVERSE REACTIONS: Adverse event information is derived from controlled clinical trials and worldwide marketing experience. In the description below, rates of the more common events represent US/Canadian clinical study results. Less frequent events are derived principally from marketing experience in approximately 7 million patients and from publications; there are insufficient data to support an accurate estimate of their incidence rates.

The following estimates of adverse events for DIPRIVAN Injection are derived from reports of 1573 patients included in the US/Canadian induction and maintenance studies. These studies were conducted using a variety of premedicants, varying lengths of surgical procedures and various other anesthetic agents. Most adverse events were mild and transient.

The following adverse events were reported in patients treated with DIPRIVAN Injection. They are presented within each body system in order of decreasing frequency.

Incidence Greater than 1% – All events regardless of causality, derived from clinical trials

Body as a Whole: Fever. **Cardiovascular:** Hypotension* (see also CLINICAL PHARMACOLOGY), Bradycardia, Hypertension. **Central Nervous System:** Movement,* Headache, Dizziness, Twitching, Bucking/Jerking/Thrashing, Clonic/Myoclonic Movement. **Digestive:** Nausea,** Vomiting,* Abdominal Cramping. **Injection Site:** Burning/Stinging,** Pain,** Tingling/Numbness, Coldness. **Respiratory:** Cough, Hiccough, Apnea (see also CLINICAL PHARMACOLOGY). **Skin and Appendages:** Flushing.

Incidence of unmarked events is 1%-3%; *3% to 10%; **10% or greater.

Incidence Less than 1% – Causal Relationship Probable (Adverse events reported only in the literature, not seen in clinical trials, are *italicized.*)

Body as a Whole: Extremities Pain, Chest Pain, Neck Stiffness, Trunk Pain. **Cardiovascular:** Tachycardia, Premature Ventricular Contractions, Premature Atrial Contractions, Syncope, Abnormal ECG, ST Segment Depression. **Central Nervous System:** Shivering, Somnolence, Hypertonia/Dystonia, Paresthesia, Tremor, Abnormal Dreams, Agitation, Confusion, Delirium, Euphoria, Fatigue, Moaning, Rigidity. **Digestive:** Hypersalivation, Dry Mouth, Swallowing. **Injection Site:** Discomfort, Phlebitis, Hives/Itching, Redness/Discoloration.

Musculoskeletal: Myalgia. **Respiratory:** Upper Airway Obstruction, Bronchospasm, Dyspnea, Wheezing, Hypoventilation, Burning in Throat, Sneezing, Tachypnea, Hyperventilation, Hypoxia. **Skin and Appendages:** Rash, Urticaria. **Special Senses:** Amblyopia, Diplopia, Eye Pain, Taste Perversion, Tinnitus. **Urogenital:** Urine Retention, *Green Urine.*

Incidence Less than 1%—Causal Relationship Unknown (Adverse events reported only in the literature, not seen in clinical trials, are *italicized.)*

Cardiovascular: Arrhythmia, Bigeminy, Edema, Ventricular Fibrillation, *Heart Block, Myocardial Ischemia.* **Central Nervous System:** Anxiety, Emotional Lability, Depression, Hysteria, Insomnia, Generalized and Localized Seizures, *Opisthotonus.* **Digestive:** Diarrhea. **Respiratory:** Laryngospasm. **Skin and Appendages:** Diaphoresis, Pruritus, *Conjunctival Hyperemia.* **Special Senses:** Ear Pain, *Nystagmus.* **Urogenital:** Abnormal Urine.

DRUG ABUSE AND DEPENDENCE: None known.

OVERDOSAGE: To date, there is no known case of acute overdosage, and no specific information on emergency treatment of overdosage is available. If accidental overdosage occurs, DIPRIVAN Injection administration should be discontinued immediately. Overdosage is likely to cause cardiorespiratory depression. Respiratory depression should be treated by artificial ventilation with oxygen. Cardiovascular depression may require repositioning of the patient by raising the patient's legs, increasing the flow rate of intravenous fluids and administering pressor agents and/or anticholinergic agents.

The intravenous LD_{50} values are 53 mg/kg in mice and 42 mg/kg in rats.

DOSAGE AND ADMINISTRATION: Induction: Dosage should be individualized and titrated to the desired effect according to the patient's age and clinical status. Most adult patients under 55 years of age and classified ASA I and II are likely to require 2.0 to 2.5 mg/kg of DIPRIVAN Injection, for induction when unpremedicated or when premedicated with oral benzodiazepines or intramuscular narcotics. For induction, DIPRIVAN Injection should be titrated (approximately 40 mg every 10 seconds) against the response of the patient until the clinical signs show the onset of anesthesia.

It is important to be familiar and experienced with the intravenous use of DIPRIVAN Injection before treating elderly, debilitated, hypovolemic patients and/or those in ASA Physical Status Classes III or IV. These patients may be more sensitive to the effects of DIPRIVAN Injection; therefore, the dosage of DIPRIVAN Injection should be decreased in these patients by approximately 50% (20 mg every 10 seconds) according to their conditions and responses. (See PRECAUTIONS, and DOSAGE GUIDE.)

Additionally, as with most anesthetic agents, the effects of DIPRIVAN Injection may be increased in patients who have received intravenous sedative or narcotic premedications shortly prior to induction.

Maintenance: Anesthesia can be maintained by administering DIPRIVAN Injection by infusion or intermittent IV bolus injection. The patient's clinical response will determine the infusion rate or the amount and frequency of incremental injections.

When administering DIPRIVAN Injection by infusion, it is recommended that drop counters, syringe pumps or volumetric pumps be used to provide controlled infusion rates.

Continuous Infusion: DIPRIVAN Injection 0.1 to 0.2 mg/kg/min administered in a variable rate infusion with 60%-70% nitrous oxide and oxygen provides anesthesia for patients undergoing general surgery. Maintenance by infusion of DIPRIVAN Injection should immediately follow the induction dose in order to provide satisfactory or continuous anesthesia during the induction phase. During this initial period following the induction injection higher rates of infusion are generally required (0.15 to 0.20 mg/kg/min) for the first 10 to 15 minutes. Infusion rates should subsequently be decreased by 30%- 50% during the first half-hour of maintenance. Changes in vital signs (increases in pulse rate, blood pressure, sweating and/or tearing) that indicate a response to surgical stimulation or lightening of anesthesia may be controlled by the administration of DIPRIVAN Injection 25 mg (2.5 mL) or 50 mg (5.0 mL) incremental boluses and/or by increasing the infusion rate. If vital sign changes are not controlled after a five minute period, other means such as a narcotic, barbiturate, vasodilator or inhalation agent therapy should be initiated to control these responses.

For minor surgical procedures (ie, body surface) 60%-70% nitrous oxide can be combined with a variable rate DIPRIVAN Injection infusion to provide satisfactory anesthesia. With more stimulating surgical procedures (ie, intra-abdominal) supplementation with analgesic agents should be considered to provide a satisfactory anesthetic and recovery profile.

Infusion rates should always be titrated downward in the absence of clinical signs of light anesthesia until a mild response to surgical stimulation is obtained in order to avoid administration of DIPRIVAN Injection at rates higher than are clinically necessary. Generally, rates of 0.05 to 0.1 mg/kg/min should be achieved during maintenance in order to optimize recovery times.

Intermittent Bolus: Increments of DIPRIVAN Injection 25 mg (2.5 mL) or 50 mg (5.0 mL) may be administered with nitrous oxide in patients undergoing general surgery. The incremental boluses should be administered when changes in vital signs indicate a response to surgical stimulation or light anesthesia.

DIPRIVAN Injection has been used with a variety of agents commonly used in anesthesia, such as atropine, scopolamine, glycopyrrolate, diazepam, depolarizing and nondepolarizing muscle relaxants, and narcotic analgesics, as well as with inhalational and regional anesthetic agents. (See Drug Interactions.)

DOSAGE GUIDE

INDICATION	DOSAGE AND ADMINISTRATION
Induction	Dosage should be individualized. **Adults:** Are likely to require 2.0 to 2.5 mg/kg (approximately 40 mg every 10 seconds until induction onset). **Elderly, Debilitated, Hypovolemic and/or ASA III or IV Patients:** Are likely to require 1.0 to 1.5 mg/kg (approximately 20 mg every 10 seconds until induction onset).
Maintenance Infusion	**Variable rate infusion**—titrated to the desired clinical effect. **Adults:** Generally, 0.1 to 0.2 mg/kg/min (6 to 12 mg/kg/h). **Elderly, Debilitated, Hypovolemic and/or ASA III or IV Patients:** Generally, 0.05 to 0.1 mg/kg/min (3 to 6 mg/kg/h).
Intermittent Bolus	Increments of 25 mg to 50 mg, as needed.

Compatibility and Stability: DIPRIVAN Injection should not be mixed with other therapeutic agents prior to administration.

Dilution Prior to Administration: When DIPRIVAN Injection is diluted prior to administration, it should only be diluted with 5% Dextrose Injection, USP, and it should not be diluted to a concentration less than 2 mg/mL because it is an emulsion. In diluted form it has been shown to be more stable when in contact with glass than with plastic (95% potency after 2 hours of running infusion in plastic.)

Administration Into a Running IV Catheter: Compatibility of DIPRIVAN Injection with the coadministration of blood/serum/plasma has not been established. (See WARNINGS.) DIPRIVAN Injection has been shown to be compatible with the following intravenous fluids when administered into a running IV catheter.

- –5% Dextrose Injection, USP
- –Lactated Ringers Injection, USP
- –Lactated Ringers and 5% Dextrose Injection
- –5% Dextrose and 0.45% Sodium Chloride Injection, USP
- –5% Dextrose and 0.2% Sodium Chloride Injection, USP

Handling Procedures: Parenteral drug products should be inspected visually for particulate matter and discoloration prior to administration whenever solution and container permit.

Do not use if there is evidence of separation of the phases of the emulsion.

Any unused portions of DIPRIVAN Injection or solutions containing DIPRIVAN Injection should be discarded at the end of the surgical procedure.

HOW SUPPLIED: DIPRIVAN Injection (NDC 0038-0290) is available in ready-to-use 20-mL ampules containing 10 mg/mL of propofol.

Store below 22°C (72°F). Do not store below 4°C (40°F). Refrigeration is not recommended. Protect from light. Shake well before use.

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Interested and qualified candidates, please send curriculum vitae to: **Mark C. Rogers, M.D., Professor & Chairman, Department of Anesthesiology and Critical Care Medicine, The Johns Hopkins Hospital, 600 N. Wolfe Street, Baltimore, Maryland 21205.**

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For Information Contact:
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